

**Heterocyclic compounds, which are inhibitors of the enzyme DPP-IV****CROSS-REFERENCE TO RELATED APPLICATIONS**

- 5 This application is a continuation of serial no 09/935149, filed August 22, 2001, now pending, which is a continuation of PCT application PCT/DK01/00467 filed July 4, 2001, and claims the benefit of US provisional application no. 60/223,240, filed August 4, 2000 and of Danish application no. PA 2000 01040 filed July 4, 2000, the contents of each of which are hereby incorporated by reference.

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**FIELD OF INVENTION**

- The present invention relates to therapeutically active and selective inhibitors of the enzyme DPP-IV, pharmaceutical compositions comprising the compounds and the use of  
15 such compounds for and the manufacture of medicaments for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity, as well as methods for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity.

**20 BACKGROUND OF THE INVENTION**

Dipeptidyl peptidase-IV (DPP-IV), a serine protease belonging to the group of post-proline/alanine cleaving amino-dipeptidases, specifically removes the two N-terminal amino acids from proteins having proline or alanine in position 2.

- Although the physiological role of DPP-IV has not been completely established, it is  
25 believed to play an important role in neuropeptide metabolism, T-cell activation, gastric ulceration, functional dyspepsia, obesity, appetite regulation, impaired fasting glucose (IFG) and diabetes.

- DPP-IV has been implicated in the control of glucose metabolism because its substrates include the insulinotropic hormones Glucagon like peptide-1 (GLP-1) and Gastric  
30 inhibitory peptide (GIP). GLP-1 and GIP are active only in their intact forms; removal of their two N-terminal amino acids inactivates them.

- In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of GLP-1 and GIP, resulting in higher plasma concentrations of these hormones, increased insulin secretion and, therefore, improved glucose tolerance. Therefore, such inhibitors  
35 have been proposed for the treatment of patients with Type 2 diabetes, a disease

characterised by decreased glucose tolerance. (Holst, J. J.; Deacon, C. F. Diabetes 47 (1998) 1663-70)

Diabetic dyslipidemia is characterized by multiple lipoprotein defects, including moderately high serum levels of cholesterol and triglycerides, small LDL particles, and low levels of HDL cholesterol. The results of recent clinical trials reveal beneficial effects of cholesterol-lowering therapy in diabetic and non-diabetic patients, thus supporting increased emphasis on treatment of diabetic dyslipidemia. The National Cholesterol Education Program's Adult Treatment Panel II advocated this need for intensive treatment of diabetic dyslipidemia.

- 10 Obesity is a well-known risk factor for the development of many very common diseases such as atherosclerosis, hypertension and diabetes. The incidence of obese people and thereby also these diseases is increasing throughout the entire industrialised world. Except for exercise, diet and food restriction no convincing pharmacological treatment for reducing body weight effectively and acceptably currently exist. However, due to its indirect but important effect as a risk factor in mortal and common diseases it will be important to find treatment for obesity or appetite regulation. Even mild obesity increases the risk for premature death, diabetes, hypertension, atherosclerosis, gallbladder disease and certain types of cancer. In the industrialised western world the prevalence of obesity has increased significantly in the past few decades. Because of the high prevalence of obesity and its health consequences, its prevention and treatment should be a high public health priority.

- At present a variety of techniques are available to effect initial weight loss. Unfortunately, initial weight loss is not an optimal therapeutic goal. Rather, the problem is that most obese patients eventually regain their weight. An effective means to establish and/or sustain weight loss is the major challenge in the treatment of obesity today.

Several compounds have been shown to inhibit DPP-IV, but all of these have limitations in relation to the potency, stability, and pharmacodynamic properties.

Such compounds have e.g. been disclosed in WO 98/19998, WO 00/34241, US 6124305 (Novartis AG) and WO 99/38501 (Trustees of Tufts University). The compounds of the

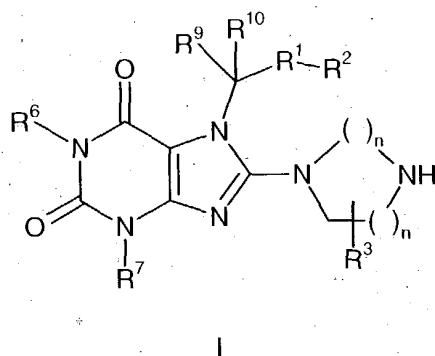
- 30 present invention constitutes a completely novel class of DPP-IV inhibitors, structurally unrelated to any DPP-IV inhibitors known so far. They are furthermore potent and stable and thus offers a solution to the problems associated with the presently known DPP-IV inhibitors.

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## SUMMARY OF THE INVENTION

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The present invention provides compounds of formula I



wherein

15 each n is one or two independently

$R^1$  is C=O; C=S; C<sub>1</sub>-C<sub>2</sub> alkyl optionally substituted with one or more  $R^4$  independently; C<sub>2</sub> alkenyl substituted with one or more  $R^4$  independently; C<sub>2</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more  $R^4$  independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more  $R^4$  independently; aryl optionally substituted with one or more  $R^4$  independently; aryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl optionally substituted with one or more  $R^4$  independently; heteroaryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more  $R^4$  independently; perhalo C<sub>1</sub>-C<sub>10</sub> alkyl; perhalo C<sub>1</sub>-C<sub>10</sub> alkyloxy;

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$R^2$  is H; C<sub>1</sub>-C<sub>7</sub> alkyl optionally substituted with one or more  $R^4$  independently; C<sub>2</sub>-C<sub>7</sub> alkenyl optionally substituted with one or more  $R^4$  independently; C<sub>2</sub>-C<sub>7</sub> alkynyl optionally substituted with one or more  $R^4$  independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with

- one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloheteroalkyl optionally substituted with one or more  $R^4$  independently; aryl optionally substituted with one or more  $R^4$  independently; aryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl optionally substituted with one or more  $R^4$  independently, -SH; -SR<sup>5</sup>; SOR<sup>5</sup>; SO<sub>2</sub>R<sup>5</sup>; -CHO; -CH(OR<sup>5</sup>)<sub>2</sub>; carboxy; -CO<sub>2</sub>R<sup>4</sup>; NHCONNH<sub>2</sub>; -NHCSNH<sub>2</sub>; -NHCONH<sub>2</sub>; -NHCOR<sup>4</sup>; -NHSO<sub>2</sub>R<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more  $R^4$  independently; cyano; nitro; halogen; hydroxy; perhalo  $C_1$ - $C_7$  alkyl; perhalo  $C_1$ - $C_7$  alkyloxy; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CSNH<sub>2</sub>; -CON<sub>2</sub>H<sub>3</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>;  $C_1$ - $C_{10}$  alkyloxy optionally substituted with  $R^4$  independently;  $C_2$ - $C_{10}$  alkenyloxy optionally substituted with  $R^4$ ;  $C_2$ - $C_{10}$  alkynyloxy optionally substituted with  $R^4$  independently, aryloxy optionally substituted with  $R^4$  independently; heteroaryloxy optionally substituted with  $R^4$  independently;
- 15  $R^3$  is H;  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^4$  independently;  $C_2$ - $C_{10}$  alkenyl optionally substituted with one or more  $R^4$  independently;  $C_2$ - $C_{10}$  alkynyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloalkyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloheteroalkyl optionally substituted with one or more  $R^4$  independently; aryl optionally substituted with one or more  $R^4$  independently; aryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-NH(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-NH(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>O-aryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>O-heteroaryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-S(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-S(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-S(CH<sub>2</sub>)<sub>1-4</sub>S-aryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-S(CH<sub>2</sub>)<sub>1-4</sub>S-heteroaryl optionally substituted with one or more  $R^4$  independently;  $C_1$ - $C_{10}$  alkyl-O-C<sub>1</sub>-C<sub>5</sub>alkyl optionally substituted with one or more  $R^4$ ; -NHCOR<sup>4</sup>; -NHSO<sub>2</sub>R<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more  $R^4$  independently; -SH; -SR<sup>5</sup>; -SOR<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; -CHO; -CH(OR<sup>5</sup>)<sub>2</sub>; carboxy; cyano; nitro; halogen; hydroxy; -SO<sub>2</sub>NH<sub>2</sub>; -
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SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>; -CSNH<sub>2</sub>; -CONHNH<sub>2</sub>; -CO<sub>2</sub>R<sup>4</sup>; -NHCNHNH<sub>2</sub>; -NHCSNH<sub>2</sub>; -NHCONH<sub>2</sub>;

R<sup>4</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl  
 5 optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more R<sup>8</sup> independently; aryl optionally substituted with one or more R<sup>8</sup> independently; heteroaryl optionally substituted with one or more R<sup>8</sup> independently; amino; amino  
 10 substituted with one or more C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>8</sup>; amino substituted with one or two aryl optionally substituted with one or more R<sup>8</sup> independently; heteroaryl optionally substituted with one or more R<sup>8</sup> independently; =O; =S; -CO-R<sup>5</sup>; -COOR<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more R<sup>8</sup> independently; NH(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl; NH(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl; -NHCOR<sup>5</sup>; -SOR<sup>5</sup>; SO<sub>2</sub>R<sup>5</sup>;  
 15 carboxy; cyano; N-hydroxyimino; nitro; halogen; hydroxy; perhalo C<sub>1</sub>-C<sub>10</sub> alkyl; perhalo C<sub>1</sub>-C<sub>10</sub> alkoxy; -SH; -SR<sup>5</sup>; -SO<sub>3</sub>H; -SO<sub>3</sub>R<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>10</sub> alkoxy optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyloxy optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyloxy optionally substituted with one or more R<sup>8</sup>  
 20 independently; aryloxy optionally substituted with one or more R<sup>8</sup> independently; heteroaryloxy optionally substituted with one or more R<sup>8</sup> independently; and two R<sup>4</sup> attached to the same carbon atom may form a spiroheterocyclic system, preferably hydantoin; thiohydantoin; oxazolidine-2,5-dione;

25 R<sup>5</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more R<sup>8</sup> independently; aryl optionally substituted with one or more R<sup>8</sup> independently; aryl  
 30 C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently; heteroaryl optionally substituted with one or more R<sup>8</sup> independently; heteroaryl C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently;

R<sup>6</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub>  
 35 alkenyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally

substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloalkyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloheteroalkyl optionally substituted with one or more  $R^4$  independently; aryl optionally substituted with one or more  $R^4$  independently; heteroaryl optionally substituted with one or more  $R^4$  independently;

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$R^7$  is H;  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^4$  independently;  $C_2$ - $C_{10}$  alkenyl optionally substituted with one or more  $R^4$  independently;  $C_2$ - $C_{10}$  alkynyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloalkyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloheteroalkyl optionally substituted with one or more  $R^4$  independently; aryl optionally substituted with one or more  $R^4$  independently; heteroaryl optionally substituted with one or more  $R^4$  independently;

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$R^8$  is H, amidoxime; nitro, tetrazole; pentafluorophenyl;  $-CH_2OH$ ;  $-CHO$ ;  $-C(OCH_3)_2$ ;  $-COCH_3$ ;  $-CF_3$ ;  $-CCl_3$ ;  $-OCF_3$ ;  $-OCH_3$ ;  $-CN$ ;  $-CO_2H$ ;  $-CO_2CH_3$ ;  $-CONH_2$ ;  $-CSNH_2$ ;  $-CON_2H_3$ ;  $-SO_3H$ ;  $-SO_2NH_2$ ;  $-SO_2NHCH_3$ ;  $-SO_2N(CH_3)_2$ ;  $-SO_2$  (1-piperazinyl);  $-SO_2$  (4-methylpiperazin-1-yl);  $-SO_2$  (pyrrolidin-1-yl);  $-SO_2$  (piperidin-1-yl);  $-SO_2$  (morpholin-4-yl); N-hydroxyimino;  $-NH_2$ ;  $-NHCH_3$ ;  $-N(CH_3)_2$ ;  $-NHCNHNH_2$ ;  $-NHCNHNHCH_3$ ;  $-NHCSNH_2$ ;  $-NHCSNHCH_3$ ;  $-NHCONH_2$ ;  $-NHCONHCH_3$ ;  $-NHCOCH_3$ ;  $-NHOSO_2CH_3$ ; piperazinyl; morpholin-4-yl; thiomorpholin-4-yl; pyrrolidin-1-yl; piperidin-1-yl; halogen;  $-OH$ ;  $-SH$ ;  $-SCH_3$ ;  $-aminoacetyl$ ;  $-OPO_3H$ ;  $-OPO_2OCH_3$ ;  $-PO_3H_2$ ;  $-PO(OCH_3)_2$ ;  $PO(OH)(OCH_3)$ ;

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$R^9$  is H; halogen;  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^4$  independently

$R^{10}$  is H; halogen;

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or,  $R^9$  and  $R^{10}$  may be connected to form a cyclopropyl ring;

or a salt thereof with a pharmaceutically acceptable acid or base;

30 with the exception of the following compounds:

1,3-dimethyl-7-(2-oxo-propyl)-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

1,3,1',3',7'-pentamethyl-8-piperazin-1-yl-3,7,3',7'-tetrahydro-7,8'-methanediyl-bis-purine-2,6-dione,

3,4,5-trimethoxy-benzoic acid 2-(1,3-dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-

35 tetrahydro-purin-7-yl)-ethyl ester,

7-[2-Hydroxy-3-(4-methoxy-phenoxy) -propyl]-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

7-[2-hydroxy-2-(4-nitro-phenyl) -ethyl]-3-methyl-8-piperazin-1-yl-3,7,8,9-tetrahydro-purine-2,6-dione,

5 7-Benzyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

7-(4-Chloro-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

7-(2-Chloro-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

7-Ethyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

3-Methyl-8-piperazin-1-yl-1,7-dipropyl-3,7-dihydro-purine-2,6-dione,

10 3-Methyl-7-(3-methyl-butyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

7-Butyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

3-Methyl-7-(3-phenyl-propyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

7-But-2-enyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

7-(3-Chloro-but-2-enyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

15 7-Heptyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

3-Methyl-7-(1-phenyl-ethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

3-Methyl-7-(3-methyl-benzyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

3-Methyl-7-propyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione, and

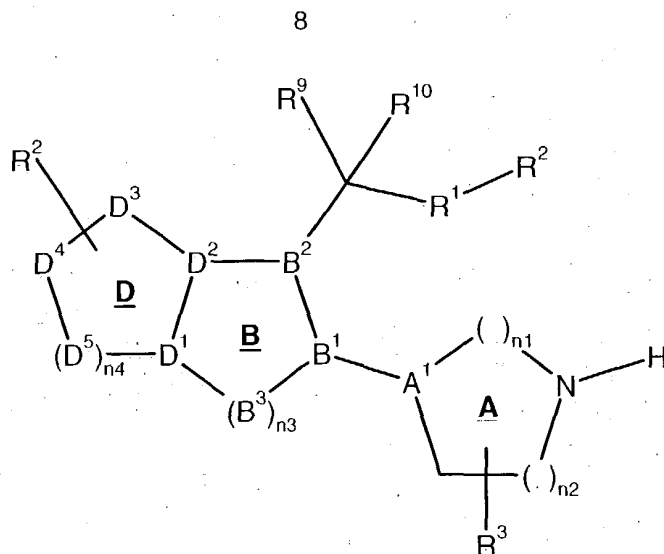
3-Methyl-7-pentyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione.

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Compounds of formula I may be used for the manufacture of a medicament for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV.

In another aspect, the invention relates to the use of compounds of formula II

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wherein

A<sup>1</sup> is a carbon or nitrogen atom

The A-ring may be substituted with one or more R<sup>3</sup>

5 B<sup>1</sup> and B<sup>2</sup> are carbon or nitrogen atoms, independently,

each B<sup>3</sup> is a carbon, nitrogen, oxygen, or sulfur atom, independently, each n<sub>1</sub>, n<sub>2</sub>, n<sub>3</sub>, n<sub>4</sub> is one or two, independently,

D<sup>3</sup>, D<sup>4</sup>, and D<sup>5</sup> may be absent, in which case D<sup>1</sup> and D<sup>2</sup> may each be optionally substituted with one or two R<sup>2</sup>, independently,

10 D<sup>1</sup>, D<sup>2</sup>, D<sup>3</sup>, D<sup>4</sup>, and each D<sup>5</sup> may independently be a carbon, nitrogen, oxygen, or a sulfur atom, or C=O, or C=S;

the bonds in the B-ring may be saturated or unsaturated, such that the B-ring may be a five-membered or a six-membered carbocyclic or heterocyclic ring, which may be fully saturated, or partially or fully unsaturated;

15 the bonds in the D-ring, when present, may be saturated or unsaturated, such that the D-ring may be a five-membered or a six-membered carbocyclic or heterocyclic ring, which may be fully saturated, or partially or fully unsaturated;

R<sup>1</sup> is C=O; C=S; C<sub>1</sub>-C<sub>2</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub> alkenyl substituted with one or more R<sup>4</sup> independently; C<sub>2</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl

20 optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more R<sup>4</sup> independently; aryl optionally substituted with one or more R<sup>4</sup> independently; aryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; heteroaryl optionally substituted with one or more R<sup>4</sup> independently;



heteroaryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; perhalo C<sub>1</sub>-C<sub>10</sub> alkyl; perhalo C<sub>1</sub>-C<sub>10</sub> alkyloxy;

- Each R<sup>2</sup> is independently H; C<sub>1</sub>-C<sub>7</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>7</sub> alkenyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>7</sub> alkynyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more R<sup>4</sup> independently; aryl optionally substituted with one or more R<sup>4</sup> independently; aryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; heteroaryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; heteroaryl optionally substituted with one or more R<sup>4</sup> independently, -SH; -SR<sup>5</sup>; -SOR<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; -CHO; -CH(OR<sup>5</sup>)<sub>2</sub>; carboxy; -CO<sub>2</sub>R<sup>4</sup>; NHCONNH<sub>2</sub>; -NHCSNH<sub>2</sub>; -NHCONH<sub>2</sub>; -NHCOR<sup>4</sup>; -NHSO<sub>2</sub>R<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more R<sup>4</sup> independently; cyano; nitro; halogen; hydroxy; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CSNH<sub>2</sub>; -CON<sub>2</sub>H<sub>3</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>10</sub> alkyloxy optionally substituted with R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyloxy optionally substituted with R<sup>4</sup>; C<sub>2</sub>-C<sub>10</sub> alkynyloxy optionally substituted with R<sup>4</sup> independently; aryloxy optionally substituted with R<sup>4</sup> independently; heteroaryloxy optionally substituted with R<sup>4</sup> independently;
- R<sup>3</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>6</sub> cycloheteroalkyl optionally substituted with one or more R<sup>4</sup> independently; aryl optionally substituted with one or more R<sup>4</sup> independently; aryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; heteroaryl C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; heteroaryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-NH(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-NH(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>O-aryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-O(CH<sub>2</sub>)<sub>1-4</sub>O-heteroaryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-S(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-S(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-

S(CH<sub>2</sub>)<sub>1-4</sub>S-aryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-S(CH<sub>2</sub>)<sub>1-4</sub>S-heteroaryl optionally substituted with one or more R<sup>4</sup> independently; C<sub>1</sub>-C<sub>10</sub>alkyl-O-C<sub>1</sub>-C<sub>5</sub>alkyl optionally substituted with one or more R<sup>4</sup>; -NHCOR<sup>4</sup>; -NHSO<sub>2</sub>R<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more R<sup>4</sup> independently; -SH; -SR<sup>5</sup>; -SOR<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; -CHO; -CH(OR<sup>5</sup>)<sub>2</sub>; carboxy; cyano; nitro; halogen; hydroxy; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>; -CSNH<sub>2</sub>; -CONHNH<sub>2</sub>; -CO<sub>2</sub>R<sup>4</sup>; -NHCNHNH<sub>2</sub>; -NHCSNH<sub>2</sub>; -NHCONH<sub>2</sub>; -NHCOR<sup>4</sup>; -NHSO<sub>2</sub>R<sup>5</sup>;

R<sup>4</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>6</sub> cycloheteroalkyl optionally substituted with one or more R<sup>8</sup> independently; aryl optionally substituted with one or more R<sup>8</sup> independently; heteroaryl optionally substituted with one or more R<sup>8</sup> independently; amino; amino substituted with one or more C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>8</sup>; amino substituted with one or two aryl optionally substituted with one or more R<sup>8</sup> independently; heteroaryl optionally substituted with one or more R<sup>8</sup> independently; =O; =S; -CO-R<sup>5</sup>; -COOR<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more R<sup>8</sup> independently; NH(CH<sub>2</sub>)<sub>1-4</sub>NH-aryl; NH(CH<sub>2</sub>)<sub>1-4</sub>NH-heteroaryl; -NHCOR<sup>5</sup>; -SOR<sup>5</sup>; SO<sub>2</sub>R<sup>5</sup>; carboxy; cyano; N-hydroxyimino; nitro; halogen; hydroxy; perhaloalkyl; perhaloalkyloxy; -SH; -SR<sup>5</sup>; -SO<sub>3</sub>H; -SO<sub>3</sub>R<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>10</sub> alkyloxy optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyloxy optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyloxy optionally substituted with one or more R<sup>8</sup> independently; aryloxy optionally substituted with one or more R<sup>8</sup> independently; heteroaryloxy optionally substituted with one or more R<sup>8</sup> independently; two R<sup>4</sup> attached to the same carbon may form a spiroheterocyclic system such as hydantoin; thiohydantoin; oxazolidine-2,5-dione;

R<sup>5</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>8</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more R<sup>8</sup> independently; aryl optionally substituted with one or more R<sup>8</sup> independently; aryl C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently; heteroaryl optionally

substituted with one or more R<sup>8</sup> independently; heteroaryl C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with one or more R<sup>8</sup> independently;

- R<sup>8</sup> is H, amidoxime; nitro, tetrazole; pentafluorophenyl; -CH<sub>2</sub>OH; -CHO; -C(OCH<sub>3</sub>)<sub>2</sub>; -  
 5 COCH<sub>3</sub>; -CF<sub>3</sub>; -CCl<sub>3</sub>; -OCF<sub>3</sub>; -OCH<sub>3</sub>; -CN; -CO<sub>2</sub>H; -CO<sub>2</sub>CH<sub>3</sub>; -CONH<sub>2</sub>; -CSNH<sub>2</sub>; -CON<sub>2</sub>H<sub>3</sub>; -  
 SO<sub>3</sub>H; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NHCH<sub>3</sub>; -SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>; -SO<sub>2</sub> (1-piperazinyl); -SO<sub>2</sub> (-4-  
 methylpiperazin-1-yl); -SO<sub>2</sub> (pyrrolidin-1-yl); -SO<sub>2</sub> (piperidin-1-yl); -SO<sub>2</sub> (morpholin-4-yl); N-  
 hydroxyimino; -NH<sub>2</sub>; -NHCH<sub>3</sub>; -N(CH<sub>3</sub>)<sub>2</sub>; -NHCNHNH<sub>2</sub>; -NHCNHNHCH<sub>3</sub>; -NHCSNH<sub>2</sub>; -  
 NHCSNHCH<sub>3</sub>; -NHCONH<sub>2</sub>; -NHCONHCH<sub>3</sub>; -NHCOCH<sub>3</sub>; -NHCO<sub>2</sub>CH<sub>3</sub>; piperazinyl;  
 10 morpholin-4-yl; thiomorpholin-4-yl); pyrrolidin-1-yl; piperidin-1-yl; halogen; -OH; -SH; -  
 SCH<sub>3</sub>; -aminoacetyl; -OPO<sub>3</sub>H; -OPO<sub>2</sub>OCH<sub>3</sub>; -PO<sub>3</sub>H<sub>2</sub>; -PO(OCH<sub>3</sub>)<sub>2</sub>; PO(OH) (OCH<sub>3</sub>);

R<sup>9</sup> is H; halogen; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently

R<sup>10</sup> is H; halogen;

- 15 R<sub>9</sub> and R<sub>10</sub> may be connected to form a cyclopropyl ring  
 or a salt thereof with a pharmaceutically acceptable acid or base;

for the manufacture of a medicament for treating diseases that are associated with  
 proteins which are subject to inactivation by DPP-IV.

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## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

- The term "DPP-IV" as used herein is intended to mean Dipeptidyl peptidase IV (EC 3.4.14.5;  
 25 DPP-IV), also known as CD26. DPP-IV cleaves a dipeptide from the N terminus of a  
 polypeptide chain containing a proline or alanine residue in the penultimate position.

- The term "treatment" is defined as the management and care of a patient for the purpose of  
 combating the disease, condition, or disorder and includes the administration of a compound  
 of the present invention to prevent the onset of the symptoms or complications, or alleviating  
 30 the symptoms or complications, or eliminating the disease, condition, or disorder.

The term "beta cell degeneration" is intended to mean loss of beta cell function, beta cell  
 dysfunction, and death of beta cells, such as necrosis or apoptosis of beta cells.

- The term "C<sub>1</sub>-C<sub>10</sub> alkyl" as used herein, alone or in combination, refers to a straight or  
 branched, saturated hydrocarbon chain having from 1-10 carbon atoms such as but not  
 35 limited to e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec. Butyl, isobutyl, tert. Butyl, n-

pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 4-methylpentyl, neopentyl, 2,2-dimethylpropyl and the like.

The term "C<sub>2</sub>-C<sub>10</sub>-alkenyl" used herein, alone or in combination, refers to a straight or branched, unsaturated hydrocarbon chain having from 2-10 carbon atoms and at least one double bond such as but not limited to vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl and the like.

The term "C<sub>2</sub>-C<sub>10</sub> alkynyl" as used herein, alone or in combination, refers to an unsaturated hydrocarbon chain having from 2-10 carbon atoms and at least one triple bond such as but not limited to -C≡CH, -C≡CCH<sub>3</sub>, -CH<sub>2</sub>C≡CH, -CH<sub>2</sub>-CH<sub>2</sub>-C≡CH, -CH(CH<sub>3</sub>)C≡CH and the like.

The term "C<sub>1-10</sub>-alkoxy" as used herein, alone or in combination is intended to include those C<sub>1-10</sub>-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term "C<sub>3</sub>-C<sub>10</sub> cycloalkyl" as used herein refers to a radical of one or more saturated cyclic hydrocarbon having from 3-10 carbon atoms such as but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl and the like.

The term "C<sub>5</sub>-C<sub>10</sub> cycloalkenyl" as used herein refers to a radical of one or more cyclic hydrocarbon having at least one double bond having from 5-10 carbon atoms such as but not limited to cyclopentenyl, cyclohexenyl and the like

The term "C<sub>2</sub>-C<sub>6</sub> cycloheteroalkyl" as used herein refers to a radical of totally saturated heterocycle like a cyclic hydrocarbon containing one or more heteroatoms selected from nitrogen, oxygen and sulphur independently in the cycle such as pyrrolidine (1-pyrrolidine; 2- pyrrolidine; 3- pyrrolidine; 4- pyrrolidine; 5- pyrrolidine); pyrazolidine (1-pyrazolidine; 2- pyrazolidine; 3- pyrazolidine; 4-pyrazolidine; 5-pyrazolidine); imidazolidine (1- imidazolidine; 2- imidazolidine; 3- imidazolidine; 4- imidazolidine; 5- imidazolidine); thiazolidine (2- thiazolidine; 3- thiazolidine; 4- thiazolidine; 5- thiazolidine); piperidine (1- piperidine; 2- piperidine; 3- piperidine; 4- piperidine; 5- piperidine; 6- piperidine); piperazine (1- piperazine; 2- piperazine; 3- piperazine; 4- piperazine; 5- piperazine; 6- piperazine); morpholine (2- morpholine; 3- morpholine; 4- morpholine; 5- morpholine; 6- morpholine); thiomorpholine (2- thiomorpholine; 3- thiomorpholine; 4- thiomorpholine; 5- thiomorpholine; 6- thiomorpholine); 1,2-oxathiolane (3-(1,2-oxathiolane); 4-(1,2-

- oxathiolane); 5-(1,2-oxathiolane); 1,3-dioxolane (2-(1,3-dioxolane); 4-(1,3-dioxolane); 5-(1,3-dioxolane); tetrahydropyran; (2-tetrahydropyran; 3-tetrahydropyran; 4-tetrahydropyran; 5-tetrahydropyran; 6-tetrahydropyran); hexahydropyridazine (1-(hexahydropyridazine); 2-(hexahydropyridazine); 3-(hexahydropyridazine); 4-(hexahydropyridazine); 5-(hexahydropyridazine); 6-(hexahydropyridazine)).

The term "aryl" as used herein includes carbocyclic aromatic ring systems. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems. The term "heteroaryl" as used herein includes heterocyclic unsaturated ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as

10 furyl, thienyl, pyrrolyl, heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated below.

- The terms "aryl" and "heteroaryl" as used herein refers to an aryl which can be optionally substituted or a heteroaryl which can be optionally substituted and includes phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-
- 15 hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl,
- 20 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl,
- 25 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-
- 30 benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-
- 35 indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-

indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl).

The term halogen as used herein refers to fluorine, chlorine, bromine or iodine.

In the compounds of formula I,  $R^2$  is preferably H;  $C_2$ - $C_7$  alkenyl optionally substituted with one or more  $R^4$  independently;  $C_2$ - $C_7$  alkynyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloalkyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloheteroalkyl optionally substituted with one or more  $R^4$  independently; aryl optionally substituted with one or more  $R^4$  independently; aryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl optionally substituted with one or more  $R^4$  independently, -SH; -SR<sup>5</sup>; -SOR<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; -CHO; -CH(OR<sup>5</sup>)<sub>2</sub>; carboxy; -CO<sub>2</sub>R<sup>4</sup>; NHCONNH<sub>2</sub>; -NHCSNH<sub>2</sub>; -NHCONH<sub>2</sub>; -NHCOR<sup>4</sup>; -NHSO<sub>2</sub>R<sup>5</sup>; -NHCOR<sup>4</sup>; -NHSO<sub>2</sub>R<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more  $R^4$  independently; cyano; nitro; halogen; hydroxy; perhalo  $C_1$ - $C_7$  alkyl; perhalo  $C_1$ - $C_7$  alkyloxy; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CSNH<sub>2</sub>; -CON<sub>2</sub>H<sub>3</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>;  $C_1$ - $C_{10}$  alkyloxy optionally substituted with  $R^4$  independently;  $C_2$ - $C_{10}$  alkenyloxy optionally substituted with  $R^4$ ;  $C_2$ - $C_{10}$  alkynyloxy optionally substituted with  $R^4$  independently, aryloxy optionally substituted with  $R^4$  independently; heteroaryloxy optionally substituted with  $R^4$  independently.

More specifically, in the compounds of formula I,  $R^2$  may be H;  $C_3$ - $C_7$  cycloalkyl optionally substituted with one or more  $R^4$  independently;  $C_3$ - $C_7$  cycloheteroalkyl optionally substituted with one or more  $R^4$  independently; aryl optionally substituted with one or more  $R^4$  independently; aryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl  $C_1$ - $C_3$  alkyl optionally substituted with one or more  $R^4$  independently; heteroaryl optionally substituted with one or more  $R^4$  independently, -SH; -

SR<sup>5</sup>; SOR<sup>5</sup>; SO<sub>2</sub>R<sup>5</sup>; -CHO; -CH(OR<sup>5</sup>)<sub>2</sub>; carboxy; -CO<sub>2</sub>R<sup>4</sup>; NHCONNH<sub>2</sub>; -NHCSNH<sub>2</sub>; -NHCONH<sub>2</sub>; -NHCOR<sup>4</sup>; -NHCO<sub>2</sub>R<sup>5</sup>; -O-CO-(C<sub>1</sub>-C<sub>5</sub>) alkyl optionally substituted with one or more R<sup>4</sup> independently; cyano; nitro; halogen; hydroxy; perhalo C<sub>1</sub>-C<sub>7</sub> alkyl; perhalo C<sub>1</sub>-C<sub>7</sub> alkyloxy; -SO<sub>2</sub>NH<sub>2</sub>; -SO<sub>2</sub>NH(R<sup>5</sup>); -SO<sub>2</sub>(R<sup>5</sup>)<sub>2</sub>; -CONH<sub>2</sub>; -CSNH<sub>2</sub>; -CON<sub>2</sub>H<sub>3</sub>; -CONH(R<sup>5</sup>); -CON(R<sup>5</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>10</sub> alkyloxy optionally substituted with R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyloxy optionally substituted with R<sup>4</sup>; C<sub>2</sub>-C<sub>10</sub> alkynyloxy optionally substituted with R<sup>4</sup> independently; aryloxy optionally substituted with R<sup>4</sup> independently; heteroaryloxy optionally substituted with R<sup>4</sup> independently.

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Alternatively, in the compounds of formula I, R<sup>2</sup> may be H. In this embodiment, R<sup>1</sup> may preferably be C=O; C=S; C<sub>1</sub>-C<sub>2</sub> alkyl substituted with one or more R<sup>4</sup> independently; C<sub>2</sub> alkenyl substituted with one or more R<sup>4</sup> independently; C<sub>2</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more R<sup>4</sup> independently; aryl substituted with one or more R<sup>4</sup> independently; aryl C<sub>1</sub>-C<sub>3</sub> alkyl substituted with one or more R<sup>4</sup> independently; heteroaryl substituted with one or more R<sup>4</sup> independently; heteroaryl C<sub>1</sub>-C<sub>3</sub> alkyl substituted with one or more R<sup>4</sup> independently.

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In the compounds of formula I, R<sup>9</sup> is preferably H, and R<sup>10</sup> is preferably H.

In the compounds of formula I, R<sup>6</sup> and R<sup>7</sup> may independently be H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl optionally substituted with one or more R<sup>4</sup> independently; heteroaryl optionally substituted with one or more R<sup>4</sup> independently. In particular, R<sup>6</sup> and R<sup>7</sup> may independently be H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently. More particularly, R<sup>6</sup> and R<sup>7</sup> may independently be H; C<sub>1</sub>-C<sub>10</sub> alkyl.

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When R<sup>10</sup> is H, R<sup>6</sup> and R<sup>7</sup> may independently be H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one or more R<sup>4</sup> independently.

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In the compounds of formula I, R<sup>4</sup> may be piperidino optionally substituted with one or more R<sup>8</sup> independently; piperazino optionally substituted with one or more R<sup>8</sup> independently; morpholino optionally substituted with one or more R<sup>8</sup> independently; thiomorpholino optionally substituted with one or more R<sup>8</sup> independently; pyrrolidino optionally substituted with one or more R<sup>8</sup> independently. In this embodiment, R<sup>6</sup> and R<sup>7</sup> may independently be H; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkenyl optionally substituted with one or more R<sup>4</sup> independently; C<sub>2</sub>-C<sub>10</sub> alkynyl optionally substituted with one or more R<sup>4</sup> independently.

### 10 Preferred Compounds

- 7-Benzyl-8-(6-hydroxymethyl-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione.
- 7-Benzyl-8-(6-hydroxy-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 7-Benzyl-8-(3-hydroxymethyl-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 7-Benzyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 15 1,3-Dimethyl-7-(4-methylbenzyl) -8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 3-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzonitrile
- 2-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzonitrile
- 1,3-Dimethyl-7-(1-phenylethyl) -8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 7-(2-Iodobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 20 1,3-Dimethyl-8-piperazin-1-yl-7-(2-trifluoromethylbenzyl) -3,7-dihydropurine-2,6-dione
- 1,3-Dimethyl-7-naphthalen-1-ylmethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 1,3-Dimethyl-7-naphthalen-2-ylmethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 7-(3-Bromobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 7-Benzyl-8-(3-isopropylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 25 7-Benzyl-8-[1,4]diazepan-1-yl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- 1,3-Dimethyl-7-(2-oxo-2-pyrrolidin-1-yl-ethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 2-(8-[1,4]Diazepan-1-yl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl) -benzonitrile
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- 7-(2-Difluoromethoxy-benzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 30 7-(2,3-Dimethoxy-benzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 1,3-Dimethyl-8-piperazin-1-yl-7-(2-trifluoromethoxy-benzyl) -3,7-dihydro-purine-2,6-dione
- 1,3-Dimethyl-8-piperazin-1-yl-7-(2-trifluoromethylsulfanyl-benzyl) -3,7-dihydro-purine-2,6-dione
- 4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydro-purin-7-yl) -butyronitrile
- R) -7-Benzyl-8-(3-isopropylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 35 S) -7-Benzyl-8-(3-isopropylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 7-Benzyl-8-(6,9-diazaspiro[4.5]dec-9-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 7-Benzyl-8-(piperazin-3-spiro-3'-bicyclo[2.2.1]heptane-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione



- 8-[1,4]Diazepan-1-yl-7-(2-methoxy-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione  
 8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-naphthalen-1-ylmethyl-3,7-dihydro-purine-2,6-dione  
 8-[1,4]Diazepan-1-yl-7-(2-fluoro-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione  
 8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-methyl-benzyl) -3,7-dihydro-purine-2,6-dione  
 5 7-(2-Chloro-benzyl) -8-[1,4]diazepan-1-yl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione  
 7-(2-Bromo-benzyl) -8-[1,4]diazepan-1-yl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione  
 8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-trifluoromethyl-benzyl) -3,7-dihydro-purine-2,6-dione  
 8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-nitro-benzyl) -3,7-dihydro-purine-2,6-dione  
 3-Benzyl-8-piperazin-1-yl-7-(2-trifluoromethyl-benzyl) -3,7-dihydro-purine-2,6-dione  
 10 3,7-Dibenzyl-1-(2-hydroxy-ethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione  
 3-Benzyl-7-phenethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione  
 3,7-Dibenzyl-8-[1,4]diazepan-1-yl-3,7-dihydro-purine-2,6-dione  
 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione  
 3,7-Dibenzyl-8-[1,4]diazepan-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione  
 15 3,7-Dibenzyl-8-[1,4]diazepan-1-yl-1-(2-hydroxy-ethyl) -3,7-dihydro-purine-2,6-dione  
 2-(3,7-Dibenzyl-8-[1,4]diazepan-1-yl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl) -*N,N*-diethyl-  
 acetamide  
 1,3,7-Tribenzyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione  
 1,3,7-Tribenzyl-8-[1,4]diazepan-1-yl-3,7-dihydro-purine-2,6-dione  
 20 (S) -7-Benzyl-8-(3-benzyloxymethylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione  
 3,7-Dibenzyl-8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione  
 3,7-Dibenzyl-8-[1,4]diazepan-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione  
 3,7-Dibenzyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione  
 3,7-Dibenzyl-8-[1,4]diazepan-1-yl-3,7-dihydro-purine-2,6-dione  
 25 2-(3-Benzyl-2,6-dioxo-8-piperazin-1-yl-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) -benzonitrile  
 2-(3-Benzyl-8-[1,4]diazepan-1-yl-2,6-dioxo-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) -  
 benzonitrile  
 2-(3-Benzyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydro-purin-7-ylmethyl) -benzonitrile  
 2-(3-Benzyl-8-[1,4]diazepan-1-yl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl) -benzonitrile  
 30 3-Benzyl-7-(2-iodo-benzyl) -8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione  
 3-Benzyl-8-[1,4]diazepan-1-yl-7-(2-iodo-benzyl) -1-propyl-3,7-dihydro-purine-2,6-dione  
 3-Benzyl-7-(2-iodo-benzyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione  
 3-Benzyl-8-[1,4]diazepan-1-yl-7-(2-iodo-benzyl) -3,7-dihydro-purine-2,6-dione  
 7-Benzyl-3-methyl-8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione  
 35 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-propyl-3,7-dihydro-purine-2,6-dione  
 7-Benzyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione  
 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione  
 2-(3-Methyl-2,6-dioxo-8-piperazin-1-yl-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) -benzonitrile

- 2-(8-[1,4]Diazepan-1-yl-3-methyl-2,6-dioxo-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) – benzonitrile
- 2-(8-[1,4]Diazepan-1-yl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl) – benzonitrile
- 7-(2-Iodo-benzyl) -3-methyl-8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione
- 5 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -3-methyl-1-propyl-3,7-dihydro-purine-2,6-dione
- 7-(2-Iodo-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione
- 3-Benzyl-8-[1,4]diazepan-1-yl-1-(3-hydroxy-propyl) -7-(2-iodo-benzyl) -3,7-dihydro-purine-2,6-dione
- 3-Benzyl-8-[1,4]diazepan-1-yl-1-(2-ethoxy-ethyl) -7-(2-iodo-benzyl) -3,7-dihydro-purine-2,6-dione
- 10 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(3-phenyl-allyl) -3,7-dihydro-purine-2,6-dione
- 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(2-oxo-2-phenyl-ethyl) -3,7-dihydro-purine-2,6-dione
- 2-(7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-ylmethyl) – benzonitrile
- (7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl) – acetonitrile
- 15 3-Methyl-7-(2-methyl-thiazol-4-ylmethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-3-methyl-7-(2-methyl-thiazol-4-ylmethyl) -3,7-dihydro-purine-2,6-dione
- 3-Methyl-7-(2-oxo-2-phenyl-ethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-3-methyl-7-(2-oxo-2-phenyl-ethyl) -3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-3-methyl-7-phenethyl-3,7-dihydro-purine-2,6-dione
- 20 8-[1,4]Diazepan-1-yl-1-(3-hydroxy-propyl) -7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione
- 1-(3-Hydroxy-propyl) -7-(2-iodo-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(2-ethoxy-ethyl) -7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione
- 1-(2-Ethoxy-ethyl) -7-(2-iodo-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 25 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -3-methyl-1-(2-phenoxy-ethyl) -3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -1-[2-(2-methoxy-ethoxy) -ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione
- 7-(2-Iodo-benzyl) -1-[2-(2-methoxy-ethoxy) -ethyl]-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 30 8-[1,4]Diazepan-1-yl-1-(3,5-dimethoxy-benzyl) -7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -1-(3-methoxy-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione
- 7-Biphenyl-2-ylmethyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione
- 35 7-(2-Bromo-benzyl) -8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione
- 7-(2-Chloro-benzyl) -8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione
- 7-Benzyl-8-(3,5-dimethyl-piperazin-1-yl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- 7-(4-Methoxybenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione

- (1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-yl) -phenylacetic acid methyl ester
- 7-(5-Chloro-2-nitrobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzonitrile
- 5 7-(4-Methanesulfonylbenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 7-(2-Fluoro-6-nitrobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 7-(4-Benzoyloxybenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 7-(2,4-Dichlorobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 1,3-Dimethyl-8-piperazin-1-yl-7-(4-trifluoromethylbenzyl) -3,7-dihydropurine-2,6-dione
- 10 7-Biphenyl-4-ylmethyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 3-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzoic acid methyl ester
- 4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzoic acid methyl ester
- 15 7-Biphenyl-2-ylmethyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 7-(4-tert-Butylbenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 1,3-Dimethyl-8-piperazin-1-yl-7-(4-trifluoromethoxybenzyl) -3,7-dihydropurine-2,6-dione
- 7-(3,4-Dichlorobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione
- 1,3-Dimethyl-8-piperazin-1-yl-7-(4-[1,2,3]thiadiazol-4-ylbenzyl) -3,7-dihydropurine-2,6-dione
- 20 4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) -3-methoxybenzoic acid methyl ester
- 7-Cyclohexylmethyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 7-Benzyl-8-(2,5-diaza-bicyclo[2.2.1]hept-2-yl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- 8-(6-Benzyl-[1,4]diazepan-1-yl) -7-(2-iodo-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- 25 (S) -7-Benzyl-8-(3-hydroxymethylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-oxo-2-pyrrolidin-1-yl-ethyl) -3,7-dihydro-purine-2,6-dione
- 7-(2-Iodo-benzyl)-1,3-dimethyl-8-(6-pyridin-2-ylmethyl-[1,4]diazepan-1-yl)-3,7-dihydro-purine-2,6-dione
- 7-(2-Bromo-benzyl)-1,3-dimethyl-8-(6-pyridin-2-ylmethyl-[1,4]diazepan-1-yl)-3,7-dihydro-purine-2,6-dione
- 30 dione
- (S) 7-Benzyl-8-(3-benzyl-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- 7-Benzyl-1,3-dimethyl-8-(3-phenethyl-piperazin-1-yl)-3,7-dihydro-purine-2,6-dione
- (R)-7-Benzyl-8-(3-benzylpiperazin-1-yl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione
- 7-Benzyl-8-(3-(2-hydroxy-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- 35 7-Benzyl-8-(3-(2-methoxy-benzyl)-piperazin-1-yl)1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- (R) 7-Benzyl-8-(3-(4-methoxy-benzyl)-piperazin-1-yl)1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- (R)-7-Benzyl-8-(3-(4-hydroxy-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione
- (R)-7-Benzyl-1,3-dimethyl-8-(3-(4-nitro-benzyl)-piperazin-1-yl)-3,7-dihydro-purine-2,6-dione
- (R)-7-Benzyl-8-(3-(4-fluoro-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione

- (R)-4-(4-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)-piperazin-2-ylmethyl)-benzonitrile
- (R)-6-(8-(3-Benzyl-piperazin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl)-nicotinonitrile
- 5 (R)-7-Benzyl-1,3-dimethyl-8-(3-thiazol-4-ylmethyl-piperazin-1-yl)-3,7-dihydro-purine-2,6-dione
- (R)-2-[1,3-Dimethyl-2,6-dioxo-8-(3-thiophen-2-ylmethyl-piperazin-1-yl)-1,2,3,6-tetrahydro-purin-7-ylmethyl]-benzonitrile
- 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(tetrahydro-furan-2-ylmethyl)-3,7-dihydro-purine-2,6-dione
- 10 7-Benzyl-1-(2-cyclohexyl-ethyl)-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione
- 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(5-methyl-hexyl)-3,7-dihydro-purine-2,6-dione
- 7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(3-methyl-butyl)-3,7-dihydro-purine-2,6-dione
- 7-Benzyl-8-[1,4]diazepan-1-yl-1-(2-ethoxy-ethyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-(tetrahydro-furan-2-ylmethyl)-3,7-dihydro-purine-2,6-dione
- 15 2,6-dione
- 7-(2-Iodo-benzyl)-3-methyl-8-piperazin-1-yl-1-(tetrahydro-furan-2-ylmethyl)-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-(tetrahydro-pyran-2-ylmethyl)-3,7-dihydro-purine-2,6-dione
- 20 7-(2-Iodo-benzyl)-3-methyl-8-piperazin-1-yl-1-(tetrahydro-pyran-2-ylmethyl)-3,7-dihydro-purine-2,6-dione
- 7-(2-Iodo-benzyl)-3-methyl-1-(2-phenoxy-ethyl)-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-1-(2-methoxy-ethyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 7-(2-Iodo-benzyl)-1-(2-methoxy-ethyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 25 1-(2-Benzoyloxy-ethyl)-8-[1,4]diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 1-(2-Benzoyloxy-ethyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 1-(3,5-Dimethoxy-benzyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 7-(2-Iodo-benzyl)-1-(3-methoxy-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-(3-trifluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione
- 30 2,6-dione
- 7-(2-Iodo-benzyl)-3-methyl-8-piperazin-1-yl-1-(3-trifluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(2-hydroxy-propyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(2,2-diethoxy-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 35 8-[1,4]Diazepan-1-yl-1-(2,2-dimethoxy-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(2-[1,3]dioxolan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

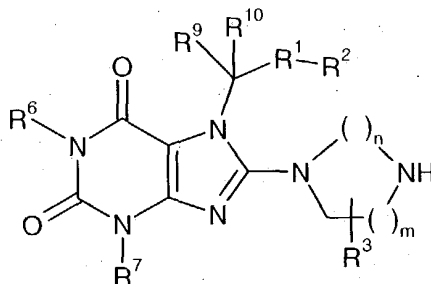
- 1-(2-[1,3]Dioxolan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 1-[1,3]Dioxolan-2-ylmethyl-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(2-[1,3]dioxan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 5 1-(2-[1,3]Dioxan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(2,3-dihydroxy-propyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 10 1-(2,3-Dihydroxy-propyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(3-hydroxy-2-methyl-propyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 1-(3-Hydroxy-2-methyl-propyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione
- 15 8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-[3-(tetrahydro-pyran-2-yloxy)-propyl]-3,7-dihydro-purine-2,6-dione
- 8-[1,4]Diazepan-1-yl-1-(2-fluoro-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 7-Benzyl-8-[1,4]diazepan-1-yl-1-(3-hydroxy-propyl)-3-methyl-3,7-dihydro-purine-2,6-dione
- 7-Biphenyl-2-ylmethyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione
- 20

In another aspect, the invention provides compounds in one of the three groups A, B and C.

25

Group A:

In the compounds of group A, the invention provides compounds of formula I



wherein

n and m is one or two independently;

- 5  $R^1$  is C=O; C=S; C<sub>1</sub>-C<sub>2</sub> alkyl; C<sub>2</sub> alkenyl; C<sub>2</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, wherein each alkyl, alkenyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, or heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl is optionally substituted with one or more  $R^4$  independently;
- 10  $R^2$  is H; C<sub>1</sub>-C<sub>7</sub> alkyl; C<sub>2</sub>-C<sub>7</sub> alkenyl; C<sub>2</sub>-C<sub>7</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; cyano; halogen; hydroxy, nitro; -SH; -SR<sup>5</sup>; -SOR<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; carboxy; -CO<sub>2</sub>R<sup>4</sup>; -CON(R<sup>5</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>10</sub> alkyloxy; C<sub>2</sub>-C<sub>10</sub> alkenyloxy; C<sub>2</sub>-C<sub>10</sub> alkynyloxy, aryloxy; heteroaryloxy, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl,
- 15 alkyloxy; alkenyloxy; alkynyloxy, aryloxy, or heteroaryloxy is optionally substituted with one or more  $R^{11}$  independently;
- $R^3$  is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; C<sub>1</sub>-C<sub>10</sub> alkyl-O-
- 20 C<sub>1</sub>-C<sub>5</sub>alkyl; carboxy; cyano; nitro; halogen; hydroxy; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, or alkyl-O-alkyl is optionally substituted with one or more  $R^{12}$  independently; two  $R^3$  attached to the same carbon atom may form a spiro system;
- 25  $R^4$ ,  $R^{11}$ ,  $R^{12}$ , and  $R^{17}$  are independently C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; heteroaryl; cyano; halogen; hydroxy, nitro; trifluormethyl; N(R<sup>13</sup>)<sub>2</sub>; =O; =S; C<sub>1</sub>-C<sub>10</sub> alkyloxy; C<sub>2</sub>-C<sub>10</sub> alkenyloxy; C<sub>2</sub>-C<sub>10</sub> alkynyloxy; aryloxy; heteroaryloxy, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, alkyloxy; alkenyloxy; alkynyloxy, aryloxy, or heteroaryloxy is optionally
- 30 substituted with one or more  $R^8$  independently; two  $R^4$  attached to the same carbon atom may form a spiroheterocyclic system, preferably hydantoin; thiohydantoin; oxazolidine-2,5-dione;
- $R^5$  is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub>
- 35 cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>5</sub> alkyl; heteroaryl; heteroaryl-C<sub>1</sub>-C<sub>5</sub> alkyl, wherein each

alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl alkyl, heteroaryl, or heteroaryl alkyl is optionally substituted with one or more  $R^{14}$  independently;

$R^6$  is H;  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl;  $C_2$ - $C_{10}$  alkynyl;  $C_3$ - $C_7$  cycloalkyl;  $C_3$ - $C_7$

5 cycloheteroalkyl; aryl; heteroaryl, wherein each each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl is optionally substituted with one or more  $R^{15}$  independently;

$R^7$  is H;  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl;  $C_2$ - $C_{10}$  alkynyl;  $C_3$ - $C_7$  cycloalkyl;  $C_3$ - $C_7$

10 cycloheteroalkyl; aryl; heteroaryl, wherein each each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl is optionally substituted with one or more  $R^{16}$  independently;

$R^8$ ,  $R^{14}$ ,  $R^{15}$ , and  $R^{16}$  are independently H; nitro;  $-OCH_3$ ; cyano; halogen;  $-OH$ ;  $-SH$ ;  $-SCH_3$ ;

15

$R^9$  is H; halogen;  $C_1$ - $C_{10}$  alkyl or aryl, wherein alkyl or aryl is optionally substituted with one or more  $R^{17}$  independently

$R^{10}$  is H; halogen;

20

or,  $R^9$  and  $R^{10}$  may be connected to form a cyclopropyl ring;

$R^{13}$  is H;  $C_1$ - $C_{10}$  alkyl or aryl;

25 or a salt thereof with a pharmaceutically acceptable acid or base;

with the exception of the following compounds:

1,3-dimethyl-7-(2-oxo-propyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

1,3,1',3',7'-pentamethyl-8-piperazin-1-yl-3,7,3',7'-tetrahydro-7,8'-methanediyl-bis-purine-

30 2,6-dione,

3,4,5-trimethoxy-benzoic acid 2-(1,3-dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydro-purin-7-yl)-ethyl ester,

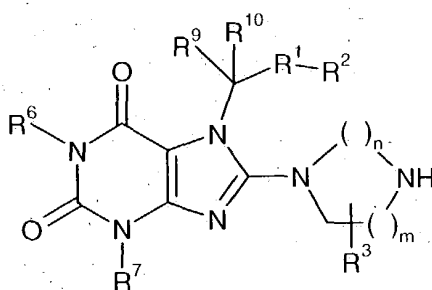
7-[2-Hydroxy-3-(4-methoxy-phenoxy) -propyl]-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,

- 7-[2-hydroxy-2-(4-nitro-phenyl) -ethyl]-3-methyl-8-piperazin-1-yl-3,7,8,9-tetrahydro-purine-2,6-dione,  
 7-Benzyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 7-(4-Chloro-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 5 7-(2-Chloro-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 7-Ethyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 3-Methyl-8-piperazin-1-yl-1,7-dipropyl-3,7-dihydro-purine-2,6-dione,  
 3-Methyl-7-(3-methyl-butyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 7-Butyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 10 3-Methyl-7-(3-phenyl-propyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 7-But-2-enyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 7-(3-Chloro-but-2-enyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 7-Heptyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 3-Methyl-7-(1-phenyl-ethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 15 3-Methyl-7-(3-methyl-benzyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione,  
 3-Methyl-7-propyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione, and  
 3-Methyl-7-pentyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione.

Group B:

20

In the compounds of group B, the invention provides compounds of formula I



I

wherein

25

n and m is one or two independently;

with the proviso that if n is 2 then m is also 2;



R<sup>1</sup> is C=O; C=S; C<sub>1</sub>-C<sub>2</sub> alkyl; C<sub>2</sub> alkenyl; C<sub>2</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, wherein each alkyl, alkenyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, or heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl is optionally substituted with one or more R<sup>4</sup> independently;

5

R<sup>2</sup> is H; C<sub>1</sub>-C<sub>7</sub> alkyl; C<sub>2</sub>-C<sub>7</sub> alkenyl; C<sub>2</sub>-C<sub>7</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; cyano; halogen; hydroxy, nitro; -SH; -SR<sup>5</sup>; -SOR<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; carboxy; -CO<sub>2</sub>R<sup>4</sup>; -CON(R<sup>5</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>10</sub> alkyloxy; C<sub>2</sub>-C<sub>10</sub> alkenyloxy; C<sub>2</sub>-C<sub>10</sub> alkynyloxy, aryloxy; heteroaryloxy, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, alkyloxy; alkenyloxy; alkynyloxy, aryloxy, or heteroaryloxy is optionally substituted with one or more R<sup>11</sup> independently;

10

R<sup>3</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; C<sub>1</sub>-C<sub>10</sub>alkyl-O-C<sub>1</sub>-C<sub>5</sub>alkyl; carboxy; cyano; nitro; halogen; hydroxy; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, or alkyl-O-alkyl is optionally substituted with one or more R<sup>12</sup> independently; two R<sup>3</sup> attached to the same carbon atom may form a spiro system;

20

R<sup>4</sup>, R<sup>11</sup>, R<sup>12</sup>, and R<sup>17</sup> are independently C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; heteroaryl; cyano; halogen; hydroxy, nitro; trifluormethyl; N(R<sup>13</sup>)<sub>2</sub>; =O; =S; C<sub>1</sub>-C<sub>10</sub> alkyloxy; C<sub>2</sub>-C<sub>10</sub> alkenyloxy; C<sub>2</sub>-C<sub>10</sub> alkynyloxy; aryloxy; heteroaryloxy, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, alkyloxy; alkenyloxy; alkynyloxy, aryloxy, or heteroaryloxy is optionally substituted with one or more R<sup>8</sup> independently; two R<sup>4</sup> attached to the same carbon atom may form a spiroheterocyclic system, preferably hydantoine; thiohydantoine; oxazolidine-2,5-dione;

25

30 R<sup>5</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>5</sub> alkyl; heteroaryl; heteroaryl-C<sub>1</sub>-C<sub>5</sub> alkyl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl alkyl, heteroaryl, or heteroaryl alkyl is optionally substituted with one or more R<sup>14</sup> independently;

R<sup>6</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; heteroaryl, wherein each each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl is optionally substituted with one or more R<sup>15</sup> independently;

5

R<sup>7</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; heteroaryl, wherein each each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl is optionally substituted with one or more R<sup>16</sup> independently;

10

R<sup>8</sup>, R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> are independently H; nitro; -OCH<sub>3</sub>; cyano; halogen; -OH; -SH; -SCH<sub>3</sub>;

R<sup>9</sup> is H; halogen; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>17</sup> independently

15 R<sup>10</sup> is H; halogen;

or, R<sup>9</sup> and R<sup>10</sup> may be connected to form a cyclopropyl ring;

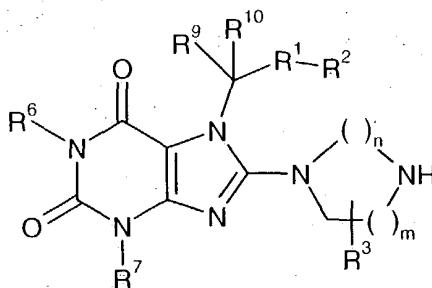
R<sup>13</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl or aryl;

20

or a salt thereof with a pharmaceutically acceptable acid or base.

#### Group C:

25 In the compounds of group C, the invention provides compounds of formula I



I

wherein

n and m is one or two independently;

R<sup>1</sup> is C=O; C=S; C<sub>1</sub>-C<sub>2</sub> alkyl; C<sub>2</sub> alkenyl; C<sub>2</sub> alkynyl ; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub>  
 5 cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, wherein each  
 alkyl, alkenyl, cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, or heteroaryl-  
 C<sub>1</sub>-C<sub>3</sub> alkyl is optionally substituted with one or more R<sup>4</sup> independently;

R<sup>2</sup> is H; C<sub>1</sub>-C<sub>7</sub> alkyl; C<sub>2</sub>-C<sub>7</sub> alkenyl; C<sub>2</sub>-C<sub>7</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl;  
 10 aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; cyano; halogen; hydroxy, nitro; -  
 SH; -SR<sup>5</sup>; -SOR<sup>5</sup>; -SO<sub>2</sub>R<sup>5</sup>; carboxy; -CO<sub>2</sub>R<sup>4</sup>; -CON(R<sup>5</sup>)<sub>2</sub>; C<sub>1</sub>-C<sub>10</sub> alkyloxy; C<sub>2</sub>-C<sub>10</sub>  
 alkenyloxy; C<sub>2</sub>-C<sub>10</sub> alkynyloxy, aryloxy; heteroaryloxy, wherein each alkyl, alkenyl, alkynyl,  
 cycloalkyl, cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl,  
 alkyloxy; alkenyloxy; alkynyloxy, aryloxy, or heteroaryloxy is optionally substituted with  
 15 one or more R<sup>11</sup> independently;

R<sup>3</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl;  
 aryl; aryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl; heteroaryl; C<sub>1</sub>-C<sub>10</sub>alkyl-O-C<sub>1</sub>-C<sub>5</sub>alkyl; carboxy;  
 cyano; nitro; halogen; hydroxy; wherein each alkyl, alkenyl, alkynyl, cycloalkyl,  
 20 cycloheteroalkyl, aryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, heteroaryl, or alkyl-O-alkyl  
 is optionally substituted with one or more R<sup>12</sup> independently; two R<sup>3</sup> attached to the same  
 carbon atom may form a spiro system;

R<sup>4</sup>, R<sup>11</sup>, R<sup>12</sup>, and R<sup>17</sup> are independently C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub>  
 25 cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; heteroaryl; cyano; halogen; hydroxy, nitro;  
 trifluormethyl; N(R<sup>13</sup>)<sub>2</sub>; =O; =S; C<sub>1</sub>-C<sub>10</sub> alkyloxy; C<sub>2</sub>-C<sub>10</sub> alkenyloxy; C<sub>2</sub>-C<sub>10</sub> alkynyloxy;  
 aryloxy; heteroaryloxy, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl,  
 aryl, heteroaryl, alkyloxy; alkenyloxy; alkynyloxy, aryloxy, or heteroaryloxy is optionally  
 substituted with one or more R<sup>8</sup> independently; two R<sup>4</sup> attached to the same carbon atom  
 30 may form a spiroheterocyclic system, preferably hydantoine; thiohydantoine; oxazolidine-  
 2,5-dione;

R<sup>5</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub>  
 cycloheteroalkyl; aryl; aryl-C<sub>1</sub>-C<sub>5</sub> alkyl; heteroaryl; heteroaryl-C<sub>1</sub>-C<sub>5</sub> alkyl , wherein each

alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aryl alkyl, heteroaryl, or heteroaryl alkyl is optionally substituted with one or more R<sup>14</sup> independently;

R<sup>6</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; heteroaryl, wherein each each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl is optionally substituted with one or more R<sup>15</sup> independently;

R<sup>7</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; heteroaryl, wherein each each alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl is optionally substituted with one or more R<sup>16</sup> independently;

R<sup>8</sup>, R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> are independently H; nitro; -OCH<sub>3</sub>; cyano; halogen; -OH; -SH; -SCH<sub>3</sub>;

R<sup>9</sup> is H; halogen; C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with one or more R<sup>17</sup> independently

R<sup>10</sup> is H; halogen;

or, R<sup>9</sup> and R<sup>10</sup> may be connected to form a cyclopropyl ring;

R<sup>13</sup> is H; C<sub>1</sub>-C<sub>10</sub> alkyl or aryl;

or a salt thereof with a pharmaceutically acceptable acid or base.

In a further embodiment of the compounds of group A, B and C, R<sup>1</sup> is C=O; C<sub>1</sub>-C<sub>2</sub> alkyl; C<sub>2</sub> alkenyl; C<sub>2</sub> alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; C<sub>3</sub>-C<sub>7</sub> cycloheteroalkyl; aryl; or heteroaryl, wherein each alkyl, alkenyl, cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl is optionally substituted with one or more R<sup>4</sup> independently.

In a further embodiment of the compounds of group A, B and C, R<sup>1</sup> is C=O; C<sub>1</sub>-C<sub>2</sub> alkyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl; aryl; or heteroaryl, wherein each alkyl, cycloalkyl, aryl, or heteroaryl is optionally substituted with one or more R<sup>4</sup> independently.

In a further embodiment of the compounds of group A, B and C,  $R^1$  is C=O or aryl optionally substituted with one or more  $R^4$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^1$  is aryl optionally substituted with one or more  $R^4$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^1$  is aryl.

In a further embodiment of the compounds of group A, B and C,  $R^1$  is phenyl.

10

In a further embodiment of the compounds of group A, B and C,  $R^2$  is H;  $C_1$ - $C_7$  alkyl;  $C_2$ - $C_7$  alkenyl;  $C_2$ - $C_7$  alkynyl;  $C_3$ - $C_7$  cycloalkyl;  $C_3$ - $C_7$  cycloheteroalkyl; aryl; heteroaryl; cyano; halogen; hydroxy, nitro; -SH; - $SR^5$ ; - $SOR^5$ ; - $SO_2R^5$ ; - $CO_2R^4$ ;  $C_1$ - $C_{10}$  alkyloxy;  $C_2$ - $C_{10}$  alkenyloxy;  $C_2$ - $C_{10}$  alkynyloxy, wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

15 cycloheteroalkyl, aryl, heteroaryl, alkyloxy, alkenyloxy, or alkynyloxy is optionally substituted with one or more  $R^{11}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^2$  is H;  $C_1$ - $C_7$  alkyl;  $C_3$ - $C_7$  cycloheteroalkyl; aryl; cyano; halogen; nitro; - $SR^5$ ; - $SO_2R^5$ ; - $CO_2R^4$ ; or  $C_1$ - $C_{10}$  alkyloxy;

20 wherein each alkyl, cycloheteroalkyl, aryl, or alkyloxy is optionally substituted with one or more  $R^{11}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^2$  is H;  $C_1$ - $C_7$  alkyl;  $C_3$ - $C_7$  cycloheteroalkyl; aryl; cyano; halogen; - $CO_2R^4$ ; or  $C_1$ - $C_{10}$  alkyloxy; wherein each alkyl,

25 cycloheteroalkyl, aryl, or alkyloxy is optionally substituted with one or more  $R^{11}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^2$  is H;  $C_1$ - $C_7$  alkyl; cyano; halogen; or  $C_1$ - $C_{10}$  alkyloxy; wherein each alkyl or alkyloxy is optionally substituted

30 with one or more  $R^{11}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^2$  is H; cyano or halogen.

35 In a further embodiment of the compounds of group A, B and C  $R^2$  is H.

In a further embodiment of the compounds of group A and B,  $R^3$  is H;  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl;  $C_2$ - $C_{10}$  alkynyl;  $C_3$ - $C_7$  cycloalkyl; aryl;  $C_1$ - $C_{10}$ alkyl-O- $C_1$ - $C_5$ alkyl; cyano; nitro; halogen; hydroxy; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or alkyl-O-alkyl is  
5 optionally substituted with one or more  $R^{12}$  independently; two  $R^3$  attached to the same carbon atom may form a spiro system.

In a further embodiment of the compounds of group A and B,  $R^3$  is H;  $C_1$ - $C_{10}$  alkyl;  $C_1$ - $C_{10}$ alkyl-O- $C_1$ - $C_5$ alkyl; hydroxy; wherein alkyl, or alkyl-O-alkyl is optionally substituted with  
10 one or more  $R^{12}$  independently; two  $R^3$  attached to the same carbon atom may form a spiro system.

In a further embodiment of the compounds of group A and B,  $R^3$  is H or  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^{12}$  independently; two  $R^3$  attached to the same  
15 carbon atom may form a spiro system.

In a further embodiment of the compounds of group A and B,  $R^3$  is H or  $C_1$ - $C_{10}$  alkyl.

In a further embodiment of the compounds of group A and B,  $R^3$  is methyl, ethyl, or  
20 isopropyl.

In a further embodiment of the compounds of group A and B,  $R^3$  is H.

In a further embodiment of the compounds of group C,  $R^3$  is  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl;  
25  $C_2$ - $C_{10}$  alkynyl;  $C_3$ - $C_7$  cycloalkyl; aryl;  $C_1$ - $C_{10}$ alkyl-O- $C_1$ - $C_5$ alkyl; cyano; nitro; halogen; hydroxy; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or alkyl-O-alkyl is optionally substituted with one or more  $R^{12}$  independently; two  $R^3$  attached to the same carbon atom may form a spiro system.

30 In a further embodiment of the compounds of group C,  $R^3$  is  $C_1$ - $C_{10}$  alkyl;  $C_1$ - $C_{10}$ alkyl-O- $C_1$ - $C_5$ alkyl; hydroxy; wherein alkyl, or alkyl-O-alkyl is optionally substituted with one or more  $R^{12}$  independently; two  $R^3$  attached to the same carbon atom may form a spiro system.

In a further embodiment of the compounds of group C,  $R^3$  is  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^{12}$  independently; two  $R^3$  attached to the same carbon atom may form a spiro system.

- 5 In a further embodiment of the compounds of group C,  $R^3$  is  $C_1$ - $C_{10}$  alkyl.

In a further embodiment of the compounds of group C,  $R^3$  is methyl, ethyl, or isopropyl

- 10 In a further embodiment of the compounds of group A, B and C,  $R^4$  is  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl;  $C_2$ - $C_{10}$  alkynyl;  $C_3$ - $C_7$  cycloalkyl; aryl; heteroaryl; cyano; halogen; hydroxy, nitro; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heteroaryl is optionally substituted with one or more  $R^8$  independently.

- 15 In a further embodiment of the compounds of group A, B and C,  $R^4$  is  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl; or  $C_2$ - $C_{10}$  alkynyl; wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more  $R^8$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^4$  is  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^8$  independently.

20

In a further embodiment of the compounds of group A, B and C,  $R^4$  is  $C_1$ - $C_{10}$  alkyl.

In a further embodiment of the compounds of group A, B and C,  $R^4$  is methyl.

- 25 In a further embodiment of the compounds of group A, B and C,  $R^5$  is H;  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl;  $C_2$ - $C_{10}$  alkynyl;  $C_3$ - $C_7$  cycloalkyl; aryl; heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heteroaryl is optionally substituted with one or more  $R^{14}$  independently.

- 30 In a further embodiment of the compounds of group A, B and C,  $R^5$  is  $C_1$ - $C_{10}$  alkyl or aryl; wherein each alkyl or aryl is optionally substituted with one or more  $R^{14}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^6$  is H;  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl;  $C_2$ - $C_{10}$  alkynyl;  $C_3$ - $C_7$  cycloalkyl; or aryl; wherein each each alkyl, alkenyl,

- 35 alkynyl, cycloalkyl, or aryl is optionally substituted with one or more  $R^{15}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^6$  is H;  $C_1$ - $C_{10}$  alkyl; or  $C_2$ - $C_{10}$  alkenyl; wherein each alkyl or alkenyl is optionally substituted with one or more  $R^{15}$  independently.

5

In a further embodiment of the compounds of group A, B and C,  $R^6$  is H or  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^{15}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^6$  is H.

10

In a further embodiment of the compounds of group A, B and C,  $R^6$  is  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^{15}$  independently.

In a further embodiment of the compounds of group A, B and C,  $R^6$  is  $C_1$ - $C_{10}$  alkyl.

15

In a further embodiment of the compounds of group A, B and C,  $R^6$  is methyl.

In a further embodiment of the compounds of group A, B and C,  $R^7$  is H;  $C_1$ - $C_{10}$  alkyl;  $C_2$ - $C_{10}$  alkenyl; or  $C_2$ - $C_{10}$  alkynyl, wherein each alkyl, alkenyl, or alkynyl is optionally substituted with one or more  $R^{16}$  independently.

20

In a further embodiment of the compounds of group A, B and C,  $R^7$  is  $C_1$ - $C_{10}$  alkyl optionally substituted with one or more  $R^{16}$  independently.

25 In a further embodiment of the compounds of group A, B and C,  $R^7$  is  $C_1$ - $C_{10}$  alkyl.

In a further embodiment of the compounds of group A, B and C,  $R^8$  is  $-OCH_3$ .

In a further embodiment of the compounds of group A, B and C,  $R^9$  is aryl.

30

In a further embodiment of the compounds of group A, B and C,  $R^{11}$  is  $C_1$ - $C_{10}$  alkyl; aryl; cyano; halogen; wherein each alkyl or aryl is optionally substituted with one or more  $R^8$  independently.

35 In a further embodiment of the compounds of group A, B and C,  $R^{11}$  is halogen.



In a further embodiment of the compounds of group A, B and C, R<sup>12</sup> is C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>2</sub>-C<sub>10</sub> alkynyl; aryl; heteroaryl; cyano; halogen; hydroxy, nitro; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl is optionally substituted with one or more R<sup>8</sup>

5 independently.

In a further embodiment of the compounds of group A, B and C, R<sup>12</sup> is aryl; heteroaryl; or hydroxy; wherein each aryl and heteroaryl is optionally substituted with one or more R<sup>8</sup> independently.

10

In a further embodiment of the compounds of group A, B and C, R<sup>12</sup> is phenyl, pyridyl, or pyrrolidinyl.

In a further embodiment of the compounds of group A, B and C, R<sup>12</sup> is hydroxy.

15

In a further embodiment of the compounds of group A, B and C, R<sup>14</sup> is halogen.

A further aspect of the invention is a pharmaceutical composition comprising, as an active  
20 ingredient, at least one compound of the invention or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

A further aspect of the invention is the use of a compound of the invention for the  
25 manufacture of a medicament for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV.

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for treatment of metabolic disorders.

30

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for blood glucose lowering.

A further aspect of the invention is the use of a compound of the invention for the  
35 manufacture of a medicament for treatment of Type 2 diabetes.

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for the treatment of impaired glucose tolerance (IGT).

- 5 A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for the treatment of impaired fasting glucose (IFG).

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for prevention of hyperglycemia.

10

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for delaying the progression of impaired glucose tolerance (IGT) to Type 2 diabetes.

- 15 A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for delaying the progression of non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes

A further aspect of the invention is the use of a compound of the invention for the

- 20 manufacture of a medicament for increasing the number and/or the size of beta cells in a mammalian subject.

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for treatment of beta cell degeneration, in particular

- 25 apoptosis of beta cells.

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for the treatment of disorders of food intake.

- 30 A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for the treatment of obesity.

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for appetite regulation or induction of satiety.

35

A further aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for the treatment of dyslipidemia.

A further aspect of the invention is the use of a compound of the invention for the  
5 manufacture of a medicament for treatment of functional dyspepsia, in particular irritable bowel syndrome.

A further aspect of the invention is a method for the treatment of diseases or disorders associated with proteins that are subject to inactivation by DPP-IV, the method comprising  
10 administering to a subject in need thereof an effective amount of a compound of the invention.

A further aspect of the invention is methods of treating the above mentioned diseases, the method comprising administering to a subject in need thereof an effective amount of a  
15 compound of the invention.

The compounds of the present invention may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and  
20 mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. Further examples of pharmaceutically acceptable  
25 inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form.

30 The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of this invention may form solvates with standard low molecular weight  
35 solvents using methods known to the skilled artisan.

It is to be understood that the invention extends to all of the stereo isomeric forms of the claimed compounds, as well as the racemates.

In the compounds of formula II, the bonds in the B-ring may be unsaturated, such that the  
 5 B-ring is a five-membered or a six-membered carbocyclic or heterocyclic ring, which is fully unsaturated.

In a preferred embodiment of the compounds of formula II,  $D^3$ ,  $D^4$  and at least one  $D^5$  are present, and  $D^1$ ,  $D^2$ ,  $D^3$ ,  $D^4$ , and each  $D^5$  may independently be a carbon, nitrogen,  
 10 oxygen, or a sulfur atom, or C=O, or C=S, and the bonds in the B-ring are unsaturated, such that the B-ring is a five-membered or a six-membered carbocyclic or heterocyclic ring, which is fully unsaturated.

When a D-ring is present in the compounds of formula II, the bonds in the D-ring are  
 15 preferably unsaturated, such that the D-ring may be a five-membered or a six-membered carbocyclic or heterocyclic ring, which is fully unsaturated.

In the compounds of formula II, each  $n_1$ ,  $n_2$ , may be one or two, independently  $n_3$  is one, and  $n_4$  is two,  
 20  $D^1$  and  $D^2$  may be carbon atoms,  $D^4$  and one of the  $D^5$  may be nitrogen atoms, and  $D^3$  and the other  $D^5$  may be C=O, or C=S, the bonds in the B-ring may be unsaturated, such that the B-ring is a five-membered carbocyclic or heterocyclic ring, which is fully unsaturated.

25 In particular, in the compounds of formula II,  $n_1$  is two and each of  $n_2$ ,  $n_3$ ,  $n_4$  is one or two, independently.

In a specific embodiment of the compound of formula II, the B-ring is a benzene ring  
 each  $n_1$ ,  $n_2$ , is one or two, independently,  
 30  $D^3$ ,  $D^4$ , and  $D^5$  are absent, such that  $D^1$  and  $D^2$  may each be optionally substituted with one  $R^2$ , independently.

#### Pharmaceutical compositions

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

- 5 Pharmaceutical compositions containing a compound of the invention of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19<sup>th</sup> Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.
- 10 Typical compositions include a compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable basic addition salt or prodrug or hydrate thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions,
- 15 conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active
- 20 compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatine, agar, pectin, acacia, stearic acid or lower alkyl
- 25 ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and
- 30 suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active

- 5 compound of the invention which inhibits the enzymatic activity of DPP-IV to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.
- 10 If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.
- 15 For nasal administration, the preparation may contain a compound of the invention which inhibits the enzymatic activity of DPP-IV, dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.
- 20 For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or

- 25 capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	250 mg
30 Colloidal silicon dioxide (Aerosil) ®	1.5 mg
Cellulose, microcryst. (Avicel) ®	70 mg
Modified cellulose gum (Ac-Di-Sol) ®	7.5 mg
Magnesium stearate	<b>Ad.</b>

- 35 Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

\*Acylated monoglyceride used as plasticizer for film coating.

5

The compounds of formula I and formula II may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of the various diseases as mentioned above, e.g. metabolic disorders, Type 2 diabetes, hyperglycemia, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), beta cell  
10 degeneration, apoptosis of beta cells, disorders of food intake, obesity, dyslipidemia, and functional dyspepsia, in particular irritable bowel syndrome. In particular, the compounds of formula I or formula II are contemplated to be useful for the prevention or treatment of Type 2 diabetes. Furthermore, the compounds of formula I or formula II may be useful for blood glucose lowering, prevention of hyperglycemia, delaying the progression of  
15 impaired glucose tolerance to Type 2 diabetes, delaying the progression of non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes, increasing the number and/or size of beta cells in a mammalian subject, or appetite regulation or induction of satiety. The mammal to be treated with a compound of formula I or formula II is preferably a human, but may also be an animal, both a domesticated animal, e.g. household pet,  
20 and non-domesticated animal such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, per day may be used. A most preferable dosage is about  
25 0.5 mg to about 250 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or  
30 veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.05 to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.05 mg to about 1000 mg, preferably from about 0.5 mg to about 250 mg of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

The invention also encompasses prodrugs of a compound of the invention which on  
5 administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of a compound of the invention which are readily convertible in vivo into a compound of the invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H.  
10 Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of a compound of the invention.

The preparation of the compounds of formula I can be done in many ways. The starting materials are either known compounds or compounds which may be prepared in analogy with the preparation of similar known compounds. A particularly useful synthesis is  
15 outlined below.

### **Combination treatments**

The invention furthermore relates to the use of a compound according to the present  
20 invention for the preparation of a medicament for use in the treatment of diabetes in a regimen which additionally comprises treatment with another antidiabetic agent. In the present context the expression "antidiabetic agent" includes compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathophysiological mechanism.

25 In one embodiment of this invention, the antidiabetic agent is insulin or GLP-1 or any analogue or derivative thereof.

In another embodiment the antidiabetic agent is a hypoglycaemic agent, preferably an oral hypoglycaemic agent.

Oral hypoglycaemic agents are preferably selected from the group consisting of  
30 sulfonylureas, non-sulphonylurea insulin secretagogues, biguanides, thiazolidinediones, alpha glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers, insulin sensitizers, hepatic enzyme inhibitors, glucose uptake modulators, compounds modifying the lipid metabolism, compounds lowering food intake, and agents acting on the ATP-dependent potassium channel of the  $\beta$ -cells.

35 Among the sulfonylureas, tolbutamide, glibenclamide, glipizide and gliclazide are preferred.



Among the non-sulphonylurea insulin secretagogues, repaglinide and nateglinide are preferred.

Among the biguanides, metformin is preferred.

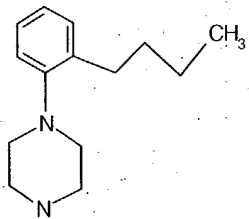
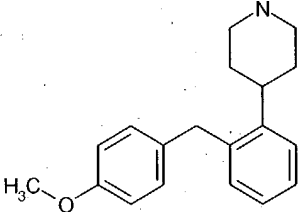
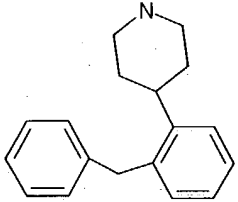
Among the thiazolidinediones, troglitazone, rosiglitazone and ciglitazone are preferred.

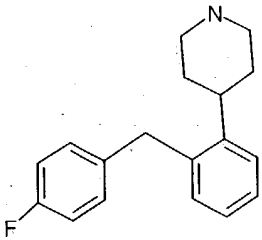
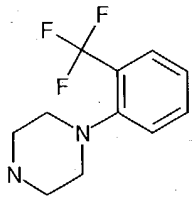
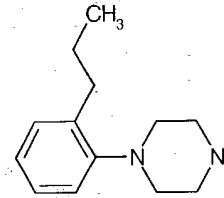
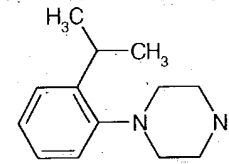
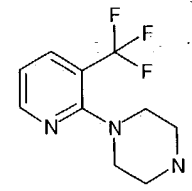
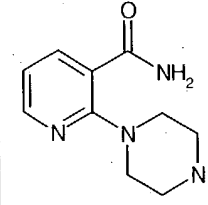
- 5 Among the glucosidase inhibitors, acarbose is preferred.

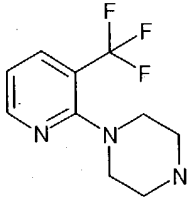
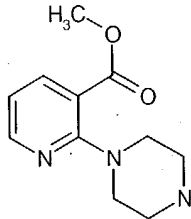
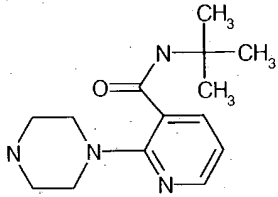
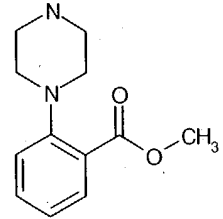
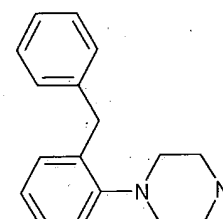
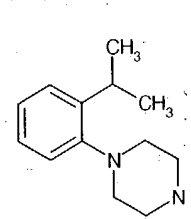
Among the agents acting on the ATP-dependent potassium channel of the  $\beta$ -cells the following are preferred: glibenclamide, glipizide, gliclazide, repaglinide.

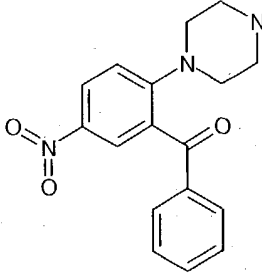
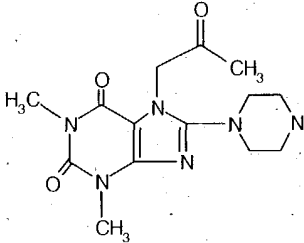
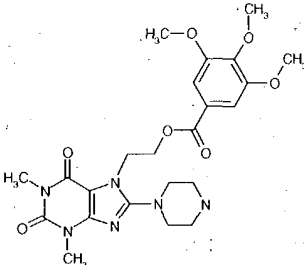
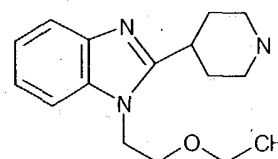
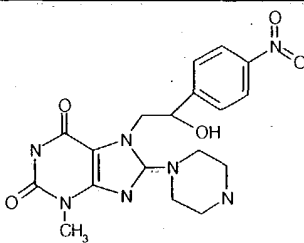
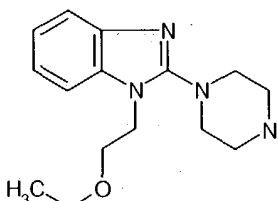
- 10 Examples from the literature of known compounds which are included in formula II are listed in Table 1 along with their Beilstein and CAS registry numbers. The synthesis methods disclosed in these references for producing compounds of general formula II are incorporated herein by reference.

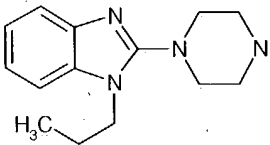
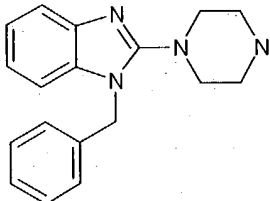
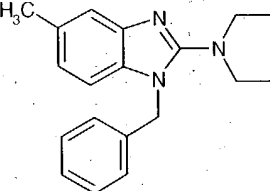
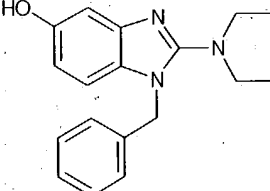
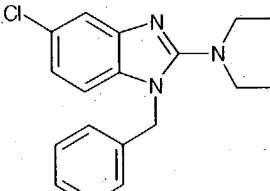
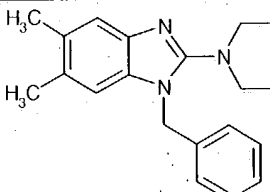
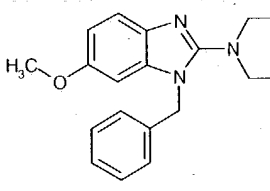
15 **Table 1**

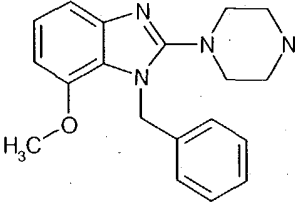
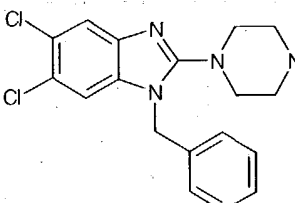
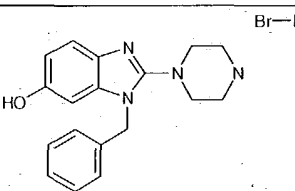
Structure	Beilstein registry number	CAS registry number
	521102	100861-48-1
	1543395	77597-74-1
	1685814	77597-48-9

 <chem>FC1=CC=C(C=C1)CCc2ccccc2N3CCNCC3</chem>	1687023	77597-75-2
 <chem>FC1(F)C(F)=CC=CC1N2CCNCC2</chem>	4189427	63854-31-9
 <chem>CC(C)c1ccccc1N2CCNCC2</chem>	4865281	119695-81-7
 <chem>CC(C)c1ccccc1N2CCNCC2</chem>	4865461	119695-82-8
 <chem>FC1(F)C(F)=C2C=CC=CN2N3CCNCC3</chem>	5667444	87394-50-1
 <chem>NC(=O)c1ccccc1N2CCNCC2</chem>	5745673	87394-64-7

 <chem>FC(F)(F)CC1=CC=CC=N1</chem>	5749933	87394-63-6
 <chem>COC(=O)C1=CC=CC=N1</chem>	6510974	104813-92-5
 <chem>CN(C)C(=O)C1=CC=CC=N1</chem>	6811251	
 <chem>CN(C)C(=O)C1=CC=CC=N1</chem>	6924778	
 <chem>CN(C)C(=O)C1=CC=CC=N1</chem>	7815919	
 <chem>CC1=CC=CC=C1N2C=CC=CC=N2</chem>	7835655	

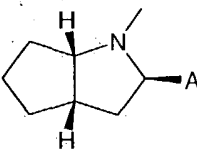
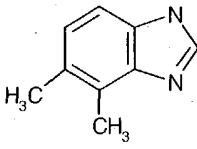
 <chem>O=[N+]([O-])c1ccc(cc1)C(=O)CN2CCNCC2</chem>	7884424	
 <chem>CC1=CNC(=C2C(=C1)N(C)C(=O)N2C)CN(C)CC3CCNCC3</chem>	1174841	24961-80-6
 <chem>COc1cc(OC(=O)OCCN2C(=O)N(C)C(=O)N2C)cc(OC)c1</chem>	1235399	20367-10-6
 <chem>CCOCCN1C(=N2C=CC=CC=C2N1)CC3CCNCC3</chem>	4698427	110963-63-8
 <chem>Oc1ccc([N+](=O)[O-])cc1CN2C(=O)N(C)C(=O)N2C3C=NC(=C2)CN(C)CC3CCNCC3</chem>	5784284	
 <chem>CCOCCN1C(=N2C=CC=CC=C2N1)CC3CCNCC3</chem>	6066512	87233-69-0

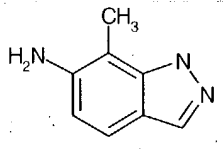
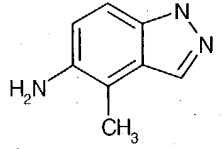
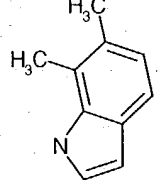
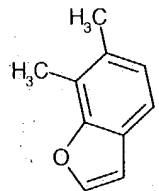
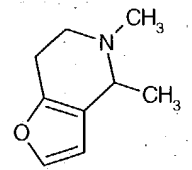
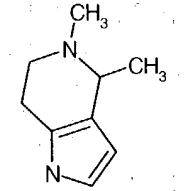
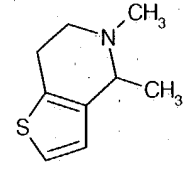
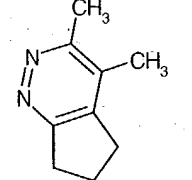
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 <chem>c1ccc(cc1)C2=CC=CC=C2N3C=NC4=CC=CC=C34C5=CC=CC=C5C6CCNCC6</chem>	7651816	
 <chem>Cc1ccc(cc1)N2C=NC3=CC=CC=C23Cc4ccccc4C5CCNCC5</chem>	7653876	
 <chem>Oc1ccc(cc1)N2C=NC3=CC=CC=C23Cc4ccccc4C5CCNCC5</chem>	7655222	
 <chem>Clc1ccc(cc1)N2C=NC3=CC=CC=C23Cc4ccccc4C5CCNCC5</chem>	7655225	
 <chem>Cc1ccc(cc1)N2C=NC3=CC=C(C)C=C32Cc4ccccc4C5CCNCC5</chem>	7656178	
 <chem>COc1ccc(cc1)N2C=NC3=CC=CC=C23Cc4ccccc4C5CCNCC5</chem>	7657431	

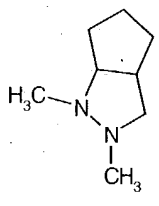
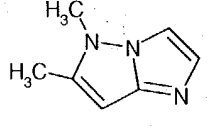
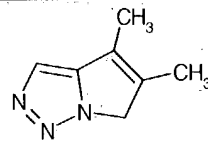
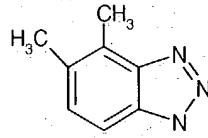
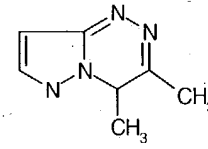
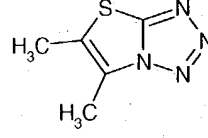
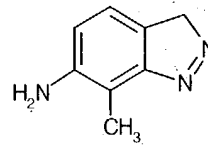
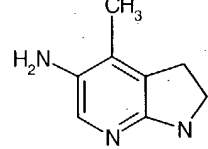
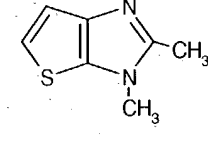
	7658569	
	7659390	
 Br-H	7675354	

Examples from the literature of the B-D ring systems of compounds of formula II shown here with only methyl or amino substituents for simplicity, includes the compounds shown in Table 2. The synthesis methods disclosed in the corresponding references for obtaining these and structurally similar compounds are incorporated herein by reference. These compounds will enable the skilled person to produce derived compounds within the scope of formula II by utilizing common general knowledge and/or the synthesis methods disclosed above.

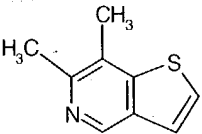
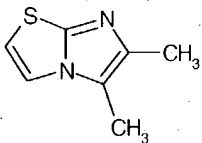
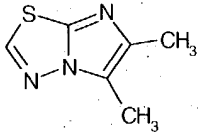
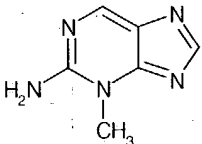
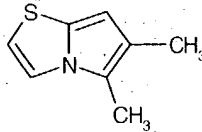
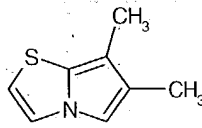
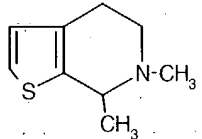
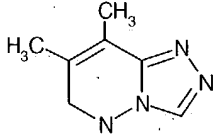
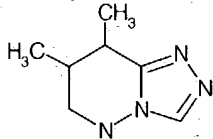
10 Table 2

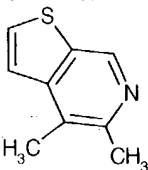
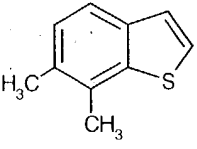
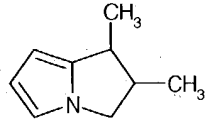
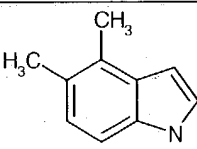
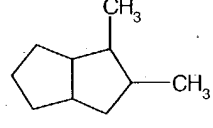
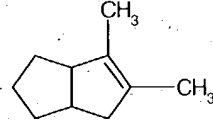
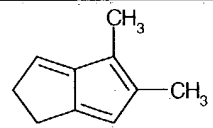
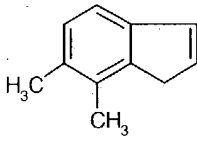
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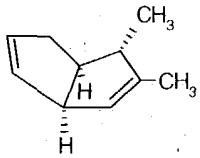
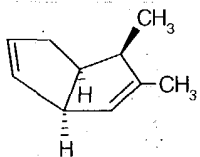
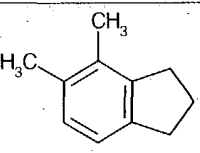
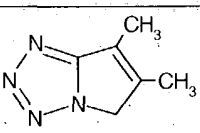
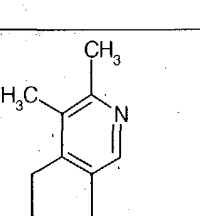
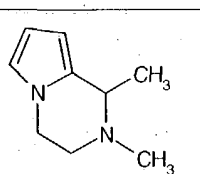
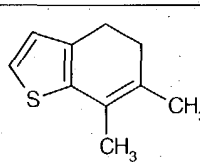
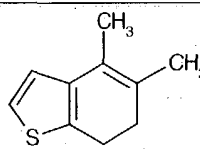
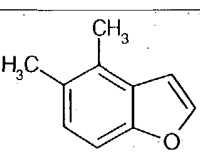
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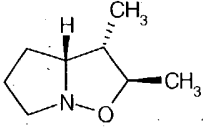
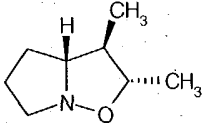
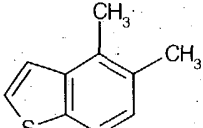
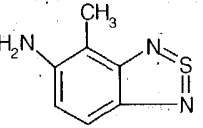
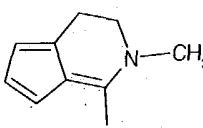
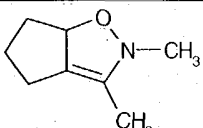
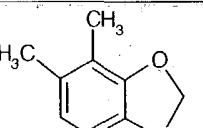
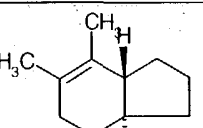
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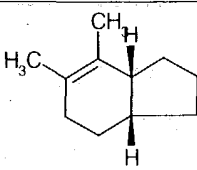
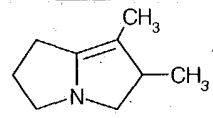
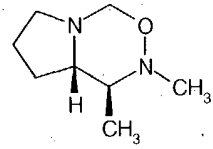


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### Methods for measuring the activity of compounds which inhibit the enzymatic activity

#### 5 of CD26/DPP-IV

##### Summary.

Chemical compounds are tested for their ability to inhibit the enzyme activity of purified CD26/DPP-IV. Briefly, the activity of CD26/DPP-IV is measured *in vitro* by its ability to cleave the synthetic substrate Gly-Pro-p-nitroanilide (Gly-Pro-pNA). Cleavage of Gly-Pro-pNA by DPP-IV liberates the product p-nitroanilide (pNA), whose rate of appearance is directly proportional to the enzyme activity. Inhibition of the enzyme activity by specific enzyme inhibitors slows down the generation of pNA. Stronger interaction between an inhibitor and the enzyme results in a slower rate of generation of pNA. Thus, the degree of inhibition of the rate of accumulation of pNA is a direct measure of the strength of enzyme inhibition. The accumulation of pNA is measured spectrophotometrically. The inhibition constant,  $K_i$ , for each compound is determined by incubating fixed amounts of enzyme with several different concentrations of inhibitor and substrate.

##### Materials:

The following reagents and cells are commercially available:

20 Porcine CD26/DPP-IV (Sigma D-7052), Gly-Pro-pNA (Sigma G0513).

Assay buffer: 50 mM Tris pH7.4, 150 mM NaCl, 0,1% Triton X-100.

##### Gly-Pro-pNA cleavage-assay for CD26:

The activity of purified CD26/DPP-IV is assayed in reactions containing:

70  $\mu$ l assay buffer

10 µl inhibitor or buffer

10 µl substrate (Gly-Pro-pNA from a 0.1M stock solution in water) or buffer

10 µl enzyme or buffer

Reactions containing identical amounts of enzyme, but varying concentrations of inhibitor

- 5 and substrate, or buffer as control, are set up in parallel in individual wells of a 96-well ELISA plate. The plate is incubated at 25°C and absorbance is read at 405 nm after 60 min incubation. The inhibitor constants are calculated by nonlinear regression hyperbolic fit and the result is expressed as inhibition constant (K<sub>i</sub>) in nM.

## 10 Diabetes model

The Zucker Diabetic Fatty (ZDF) rat model can be used to investigate the effects of the compounds of the invention on both the treatment and prevention of diabetes as rats of this sub-strain are initially pre-diabetic although develop severe type 2 diabetes

- 15 characterised by increased HbA1c levels over a period of 6 weeks. The same strain can be used to predict the clinical efficacy of other anti-diabetic drug types. For example, the model predicts the potency and limited clinical efficacy of thiazolidinedione insulin sensitiser compounds.

## 20 EXAMPLES

A further detailed description of the invention is given with reference to the following examples.

### 25 Preparative HPLC (Method A1)

Column: Waters Radial compression column Prep NovaPak c18 25x100, plus a Waters Prep NovaPak HR c18 25x10 precolumn, in a Waters PrepLC 25x100 compression module housing. Buffer: linear gradient 5 – 95 % in 15 min, MeCN, 0.1 % TFA; flow rate of 15 ml/min. The pooled fractions are either evaporated to dryness *in vacuo*, or evaporated

30 *in vacuo* until the MeCN is removed, and then frozen and freeze dried.

### Preparative HPLC (Method A2)

Column: 1.9 x 15 cm Waters XTerra RP-18. Buffer: linear gradient 5 – 95 % in 15 min, MeCN, 0.1 % TFA, flow rate of 15 ml/min. The pooled fractions are either evaporated to dryness *in vacuo*, or evaporated *in vacuo* until the MeCN is removed, and then frozen and

- 35 freeze dried.

**Preparative HPLC (Method A3)**

Column: Supelcosil ABZ+Plus, 25 cm x 10 mm, 5  $\mu$ m. Solvent A: 0.1 % TFA/Water, solvent B: MeCN. Eluent composition: 5 min. 100% A, linear gradient 0 – 100 % B in 7 min, 100% B in 2 min. Flow rate 5 ml/min. The column is allowed to equilibrate for 4 min in 5 100% A before the next run.

**HPLC-MS (Method B)**

Column: Waters Xterra MS C-18 X 3 mm id. Buffer: Linear gradient 10% - 100% in 7.5 min, MeCN, 0.01 % TFA, flow rate 1.0 ml/min. Detection 210 nm (analog output from 10 diode array detector), MS-detection ionisation mode API-ES, scan 100-1000 amu step 0.1 amu.

**HPLC-MS (Method C)**

15 The following instrumentation was used:

- Sciex API 100 Single quadropole mass spectrometer
- Perkin Elmer Series 200 Quard pump
- Perkin Elmer Series 200 autosampler
- Applied Biosystems 785A UV detector
- 20 • Sedex 55 evaporative light scattering detector
- A Valco column switch with a Valco actuator controlled by timed events from the pump.

The Sciex Sample control software running on a Macintosh PowerPC 7200 computer was used for the instrument control and data acquisition.

25

The HPLC pump was connected to four eluent reservoirs containing:

- A: Acetonitrile
- B: Water
- C: 0.5 % TFA in water
- D: 0.02 M ammonium acetate

The requirements for samples are that they contain approximately 500  $\mu$ g/ml of the 30 compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting

solvents will interfere with the chromatography at low acetonitrile concentrations.)

The analysis was performed at room temperature by injecting 20 µL of the sample solution on the column, which was eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions were used.

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µL/min (1/50) through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

The remaining 1.48 ml/min (49/50) was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following tables.

20

Column	Waters Symmetry C <sub>18</sub> 3 mm x 150 mm	
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 15 min at 1 ml/min	
Detection	UV: 214 nm	ELS: 40°C
MS	Experiment: Start: 100 amu Stop: 800 amu Step: 0.2 amu Dwell: 0.571 msec Method: Scan 284 times = 9.5 min	

#### Analytical HPLC (Method D)

Column 2.4 x 20 cm RP18. Buffer pH = 3.0 (H<sub>3</sub>PO<sub>4</sub>), Acetonitrile. Flow rate 1.0 ml/min. UV detection. Merck Hitachi system.

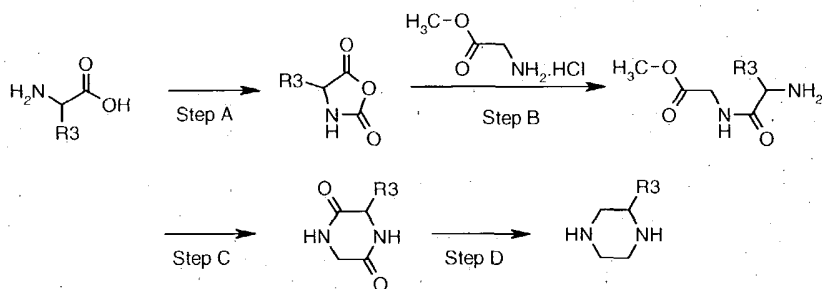
25



**General piperazine synthesis procedure I:**

The procedure is described in *Synthesis*; 3; 1984; 271-274; *Synthesis*; 12; 1981; 969-971. *Synthesis*; 10; 1982; 861-864. *Synthesis*; 4; 1991; 318-319.

5

Step A: Preparation of oxazolidine-2,5-dione derivatives:

- The amino acid (25.6 mol) was slurried in THF (100 ml) phosgene (20% in toluene)  
 10 (3.05g; 30.8 mmol) was added. The reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated *in vacuo*. The title compound precipitated as white crystals. The product was used without any further purification.

Step B: Preparation of (2-Amino-propionylamino) acetic acid methyl ester derivatives

- 15 The above oxazolidine-2,5-dione derivative (27.1mmol) dissolved in THF (50ml) was added a slurry of glycine methyl ester hydrochloride (3.75g; 29.9 mmol) and TEA (7.4g; 73.3mmol) in DCM (50ml) at 0°C. The reaction mixture was allowed to warm up to room temperature and was stirred for 15 hours. The mixture was filtered (TEA,HCl) and the reminisce was evaporated *in vacuo* giving an oil. The product was used without any  
 20 further purification.

Step C: Preparation of piperazine-2,5-dione derivatives

- The above (2-Amino-propionylamino) acetic acid methyl ester derivative (28.6 mmol) was slurried in xylene (200 ml) and refluxed (140°C) for 96 hours. A crude blackish crystalline  
 25 material was filtered of. The crystals was recrystallised from methanol and charcoal giving the title compound as white crystals.

Step D: Preparation of piperazine derivatives

The above piperazine-2,5-dione derivative (1.1 mmol) was dissolved in THF (100 ml).

LiAlH<sub>4</sub> was added in small portions under N<sub>2</sub>. The reaction mixture was stirred for 15

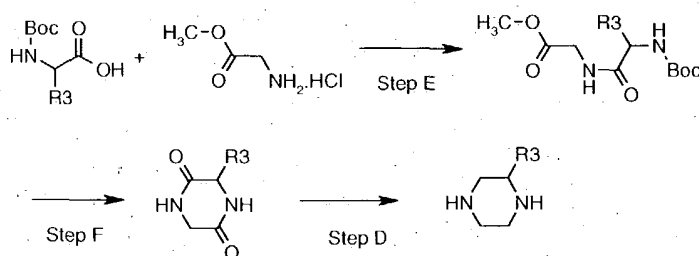
hours at 70 °C. Water was added dropwise until the mixture was white. K<sub>2</sub>CO<sub>3</sub> was added

- 5 until the mixture had a filterable consistence. The mixture was filtered evaporated *in vacuo* giving the title compound as an oil.

**General piperazine synthesis procedure II:**

Step E and F are described in *J.Org.Chem.* 50 (24); 1985; 4796-4799 while step D is as

- 10 described above.

Step E: Preparation of t-Boc-dipeptide esters:

- 15 The t-Boc-amino acid (9.4 mmol) was dissolved in dry DCM (25 ml) and 1-hydroxybenzotriazol (9.6 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (9.9 mmol) were added at 0-5 °C. Stirring was continued for ½ hour after which the amino acid methyl ester hydrochloride (10.3 mmol) and TEA (10.7 mmol) were added at 0-5 °C. The reaction mixture was stirred at room temperature overnight. The
- 20 mixture was poured into 0.5 M potassium hydrogensulphate (50 ml) and filtered. The organic phase was isolated and washed with 10 % aqueous sodium hydrogencarbonate (2 x 20 ml) and brine (1 x 20 ml), dried over magnesium sulphate and evaporated *in vacuo*. The product was used without further purification.

25 Step F: Preparation of 2,5-diketopiperazines:

The t-Boc-dipeptide methyl ester (11.6 mmol) was dissolved in formic acid (60 ml) and

stirred at room temperature for 2½ hours. The solvent was removed at 35 °C under high

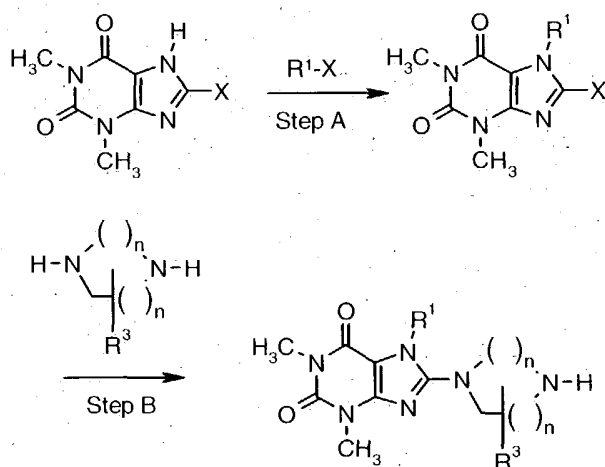
vacuum and the crude dipeptide ester formate was dissolved in a mixture of dry *sec*-butyl alcohol (24 ml) and dry toluene (12 ml). The solution was refluxed for 2 hours. After

approx. one hour the diketopiperazine start to crystallize out of the hot reaction. The reaction mixture was cooled to 0-5 °C and the white crystals of diketopiperazine was isolated by filtration.

## 5 Abbreviations

DCM	Dichloromethane
DIEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
HOAc	Acetic acid
MeCN	Acetonitrile
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TMG	Tetramethylguanidine

### General procedure (A)



R¹, R³, X and n are defined as in formula I.

#### Step A:

8-Chloro-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (Avocado, UK) (0.2g; 0.93mmol) and the arylmethylhalogenide (0.93mmol) K<sub>2</sub>CO<sub>3</sub> (0.257g; 18.6mmol) and DMF (5ml) is mixed in a scintillations vessel (20ml). The vessels are carefully sealed and the reaction mixtures

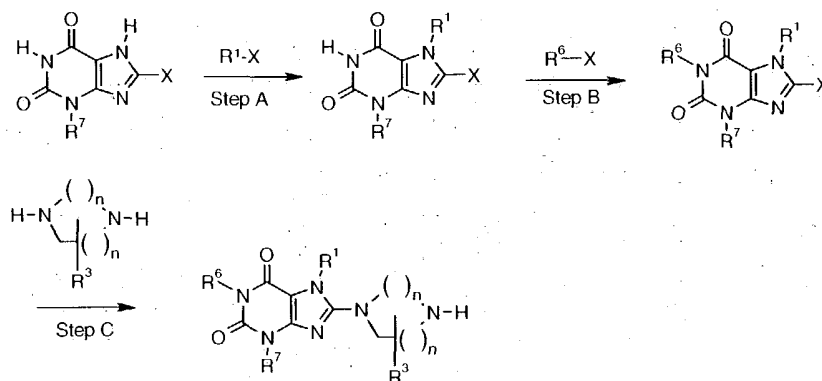
are shaken for 121 hours at 100 °C. After cooling, brine (5ml) and ethyl acetate (5ml) is added. The reaction mixtures are shaken for 10 hours. The ethyl acetate phase is decanted to a new scintillations vessel. The water/DMF-phase is then extracted with DCM (5ml). The DCM and ethyl acetate phase are combined and evaporated in a speedvac.

- 5 The residue is used without any purification in the next step.

#### Step B:

- 8-Chloro-7-(arylmethyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione derivative (50 mg, ~0.15 mmol) is dissolved in methoxyethanol (1ml) in a 4 ml scintillation vessel. The piperazine derivative (0.235mmol), and TEA (32mg; 43μL; 0.31mmol) are added. The vessels are sealed carefully and shaken for 7 days at 100 °C. The reaction mixtures are evaporated in a speedvac. Each vessel is added methanol (1ml), and 1N HCl (0.5 ml), shaken for 10 hours and evaporated in a speedvac. The samples are purified by prep. HPLC (Method A1).
- 15 The purified compounds are analysed by LC-MS.

#### General procedure (B)



- 20  $R^1$ ,  $R^3$ ,  $R^6$ ,  $R^7$ , X and n are defined as in formula I.

#### Step A

- The starting material 3-benzyl-8-bromo-3,7-dihydro-purine-2,6-dione or 3-methyl-8-bromo-3,7-dihydro-purine-2,6-dione (16 μmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 250 μL). Substituted benzyl bromide or other alkylating agents (16.8 μmol, 1.05 equiv) are dissolved in DMF (100 μL) and added. The mixture is heated to 65 °C for 2h.
- 25

Step B

Alkylation reagent R<sup>6</sup>-X (32 µmol) is dissolved in DMF (100 µl) and added to the above reaction mixture, followed by a solution of TMG in DMF (1.16 ml TMG diluted to 5.8 ml, 48 µl). The mixture is kept at 65 °C for 4h.

5

Step C

Diamine (200 µmol) is dissolved in a mixture of DMF and DIEA (3% DIEA, 200 µL) and added to the above reaction mixture. The reaction is kept at 65 °C for 1-4d.

Samples are neutralized using HOAc (20 µl). The solvent is evaporated and the residue is dissolved in DMSO/H<sub>2</sub>O (4:1, 500 µl) and purified by HPLC (Method A3).

10

**General procedure (C)**Step A:

The first reaction step is identical to Step A in general procedure (A)

15

Step B:

8-Chloro-7-(arylmethyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione derivative (1 eq.), piperazine (3 eq.) and TEA (5 eq) is heated in an appropriate solvent in a closed vessel in a micro wave oven (CEM MARSX microwave instrument. Magnetron frequency: 2455 MHz. Power Output: 1200 Watt.) at 150°C for 4 hours. The reaction mixture is cooled and evaporated *in vacuo*. The remaining oil is purified on a silica gel column with DCM/MeOH (3:1) as eluent, giving the title compound as an oil. The oil may be dissolved in DCM to afford the hydrochloride salt upon addition of hydrochloride in ether. Alternatively, the samples may be purified by prep. HPLC (Method A2). The purified compounds are analysed by LC-MS.

20

All reactions are performed in closed vessels: XP 1500 Plus Vessel set; at a given temperature in an appropriate solvent. Normally solvents like MeOH; EtOH, iPrOH; H<sub>2</sub>O; DMF and DMSO are used.

30 **General procedure (D)**Step A:

The first reaction step is identical to Step A in general procedure (A)

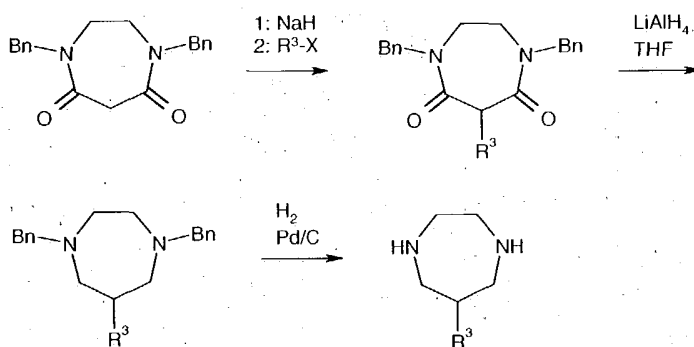
Step B:

35 8-Chloro-7-(arylmethyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione derivative (1.64

mmol), amine (2.39 mmol) and potassium carbonate (2.4 mmol) was heated in DMF (30 ml) at 100 °C for 5 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue was purified on a silica gel column (Eluent: Ethyl acetate/Methanol/Triethylamine (90:10:2)) giving the pure base. The hydrochloride salt may be prepared by dissolving the base in isopropanol and adding hydrogen chloride in diethyl ether to the solution.

### General procedure (E): Preparation of 6-substituted-[1,4]-diazepanes

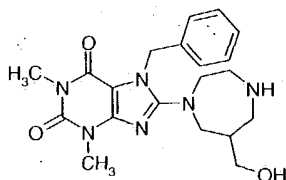
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1,4-Dibenzyl-[1,4]diazepane-5,7-dione is converted to the Na-salt in THF with NaH as base, and reacted with the R<sup>3</sup>-X alkylating reagent e.g. benzyl bromide, at room temperature. The product e.g. 1,4,6-Tribenzyl-[1,4]diazepane-5,7-dione is reduced to the 1,4,6-Tribenzyl-[1,4]diazepane by treatment with LiAlH<sub>4</sub> in THF at elevated temperature. The N-benzyl groups are removed by catalytic hydrogenation in EtOH:AcOH (1:1), using Pd/C as catalyst.

### 20 Example 1

7-Benzyl-8-(6-hydroxymethyl-[1,4]diazepan-1-yl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA



Step A: Preparation of 1,4-dibenzyl-[1,4]diazepane-6-carboxylic acid. Na-salt (1A)

*N,N*-dibenzylethylenediamine (4.9 ml, 20.8 mmol) was dissolved in toluene (200 ml), triethylamine (8.94 ml, 64.5 mmol), and methanol (20 ml) and 3-bromo-2-bromomethylpropionic acid (5.12 g, 20.8 mmol) was added. The reaction mixture was

5 heated to reflux for 24 hours. The solvents were evaporated and the remaining was redissolved in water (150 ml) and ethyl acetate (150 ml). The aqueous layer was acidified with 6N hydrochloric acid until pH=2, and the layers were separated. The aqueous layer was washed with ethyl acetate and then 10% aqueous sodium hydroxide was added until pH=12. The aqueous layer was washed with 4 x 150 ml of ethyl acetate, and then

10 evaporated to dryness. The remaining was suspended in ethyl acetate (200 ml) and dry methanol (20 ml) and salts was filtered off. The mother liquor was evaporated and purified by chromatography on silica, using 10% methanol in dichloromethane as the eluent. Fractions containing the product were evaporated, to afford 5.09 g of 1A as an yellow foam in 70% yield.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.31 (10H, m); 3.78 (4H, m); 3.18 (4H, m); 2.81 (3H, m); 2.58 (2H, m). HPLC-MS (Method B): *m/z* = 325 (M+1); *R<sub>t</sub>* = 1.55 min.

Step B: Preparation of (1,4-dibenzyl-[1,4]diazepan-6-yl)methanol (1B)

The sodium salt of 1,4-dibenzyl-[1,4]diazepane-6-carboxylic acid (1A) (2.36 g, 6.81 mmol)

20 was dissolved in dry tetrahydrofuran (50 ml) under a nitrogen atmosphere and lithium aluminium hydride (0.50 g, 13.6 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and then quenched with water until effervescence ceases. Ethyl acetate (200 ml) and solid potassium carbonate was added until a white suspension appeared, and the mixture was allowed to stir for half an hour. The suspension was

25 filtered through celite, which was washed with 3 x 50 ml of ethyl acetate. Water (200 ml) was added and the aqueous layer was extracted with 3 x 200 ml of ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was evaporated to afford 2.06 g of 1B as an yellow oil in 97% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.28 (10H, m); 3.61 (4H, s); 3.55 (2H, d); 2.99 (2H, dd); 2.73 (2H, dd);

30 2.57 (4H, m); 1.93 (1H, m). HPLC-MS (Method B): *m/z* = 311 (M+1); *R<sub>t</sub>* = 1.24 min.

Step C: Preparation of ([1,4]diazepan-6-yl)methanol (1C)

(1,4-Dibenzyl-[1,4]diazepan-6-yl)methanol (1B) (1.02 g, 3.28 mmol) was dissolved in

35 ethanol (50 ml) and acetic acid (8 ml) and palladium, 10wt.% on activated carbon (0.2 g)

was added. The mixture was hydrogenated on a Parr apparatus at 45 psi. for 6 days, and filtered twice. The solvents were evaporated and the crude product was dissolved in water (2 ml) and saturated potassium carbonate was added until pH=13. The aqueous layer was washed with 4 x 10 ml of ethyl acetate, and water was evaporated. The crude

5 product was purified by preparative HPLC (method A1;  $R_t = 2.27$  min.) to afford 5.3 g of 1C including potassium carbonate salt.

HPLC-MS (Method B):  $m/z = 131$  ( $M+1$ );  $R_t = 0.33$  min.

Step D: Preparation of 7-benzyl-8-(6-hydroxymethyl-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-

10 dihydropurine-2,6-dione. TFA (1)

[[1,4]Diazepan-6-yl)methanol (1C) including potassium carbonate salts (ca 1 mmol) was suspended in dry DMF (200 ml) and 7-benzyl-8-chloro-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (199.9 mg, 0.656 mmol) and potassium carbonate (453 mg, 3.28 mmol) were added. The reaction mixture was stirred at room temperature for 24 hours, heated to 60°C

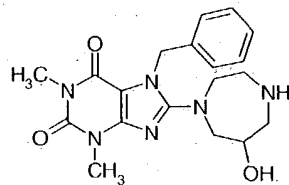
15 for 3 hours, heated to 95°C for 5 hours and heated to 120°C for 2 hours. The suspension was allowed to cool to room temperature and white salts were filtered off. The filtrate was evaporated and purified by chromatography on silica, using 5% methanol in dichloromethane as the eluent. Fractions containing the product were evaporated and purified by preparative HPLC (method A2;  $R_t = 2.52$  min.) to afford 8 mg of the title

20 compound as an yellow oil in 1% yield.

$^1\text{H-NMR}$  (MeOH- $d_4$ ):  $\delta$  7.30 (3H, m); 7.14 (2H, d); 5.53 (2H, s); 3.80-3.05 (16H, m); 2.09 (1H, m). HPLC-MS (Method B):  $m/z = 399$  ( $M+1$ );  $R_t = 1.75$  min.

**Example 2**

7-Benzyl-8-(6-hydroxy-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA



25

Step A: Preparation of 1,4-dibenzyl-[1,4]diazepan-6-ol (2A)

*N,N*-dibenzylethylenediamine (4.9 ml, 20.8 mmol) was dissolved in toluene (200 ml), triethylamine (8.94 ml, 64.5 mmol), and 1,3-dibromo-2-propanol (4.53 g, 20.8 mmol) was added. The reaction mixture was heated to reflux for 4 days. The solvents were

30 evaporated and the remaining was redissolved in water (150 ml) and ethyl acetate (150



ml). The aqueous layer was acidified with 6N hydrochloric acid until pH=2, and the layers were separated. The aqueous layer was washed with 3 x 100 ml of ethyl acetate and the combined organic material was dried with sodium sulphate, filtered and the solvent was evaporated. The crude product was purified by chromatography on silica, using 5%

- 5 methanol in dichloromethane as the eluent. Fractions containing the product were evaporated, to afford 3.59 g of 2A as an yellow oil in 59% yield.

<sup>1</sup>H-NMR (MeOH-*d*<sub>4</sub>):  $\delta$  7.30 (10H, m); 3.81 (1H, m); 3.67 (4H, s); 2.90 (2H, dd); 2.74-2.60 (6H, m). HPLC-MS (Method B):  $m/z$  = 297 (M+1);  $R_t$  = 1.49 min.

10 Step B: Preparation of [1,4]diazepan-6-ol. HOAc (2B)

1,4-Dibenzyl-[1,4]diazepan-6-ol (2A) (873 mg, 2.95 mmol) was hydrogenated for 21 days as described in example 1, step C. The reaction mixture was filtered twice, and the solvents were evaporated to afford 420 mg of 2B, as yellow crystals in 60% yield.

<sup>1</sup>H-NMR (MeOH-*d*<sub>4</sub>):  $\delta$  4.07 (1H, m); 3.61 (1H, m); 3.27-2.98 (8H, m); 1.92 (6H, s). HPLC-

- 15 MS (Method B):  $m/z$  = 117 (M+1);  $R_t$  = 0.36 min.

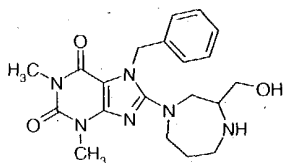
Step C: Preparation of 7-Benzyl-8-(6-hydroxy-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (2)

- [1,4]Diazepan-6-ol acetate (2B) (116 mg, 0.49 mmol) and 7-benzyl-8-chloro-1,3-dimethyl-  
20 3,7-dihydropurine-2,6-dione (100 mg, 0.33 mmol) were dissolved in 2-propanol (20 ml) and triethylamine (0.68 ml, 4.9 mmol) and the mixture was subjected to micro waves (150°C, 6 bar, 300 W, 8 hours). The solvents were evaporated and the remaining was redissolved in dichloromethane (20 ml) and water (20 ml). The aqueous layer was acidified with potassium hydrogen sulfate until pH=2. The aqueous layer was separated  
25 and aqueous sodium hydroxide was added until pH=12. The aqueous layer was extracted with 3 x 50 ml of dichloromethane, and the combined organic material were added excess trifluoroacetic acid, and evaporated, to afford 123 mg of the title compound as a brown oil in 75% yield.

- <sup>1</sup>H-NMR (MeOH-*d*<sub>4</sub>):  $\delta$  7.31 (3H, m); 7.14 (2H, m); 5.59 (2H, s); 4.23 (1H, m); 3.27-4.02  
30 (14H, m). HPLC-MS (Method B):  $m/z$  = 385 (M+1);  $R_t$  = 1.52 min.

**Example 3**

7-Benzyl-8-(3-hydroxymethyl-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA



5 Step A: Preparation of 1,4-dibenzyl-[1,4]diazepane-2-carboxylic acid methyl ester (3A)

*N,N*-Dibenzylpropane-1,3-diamine (Sandstroem, J. et al, Tetrahedron; EN; 34; 1978; 371-378) (2.0 g, 7.86 mmol), methyl 2,3-dibromopropionate (1.28 ml, 7.86 mmol), and potassium carbonate (2.17 g, 15.72 mmol) were dissolved in dry dimethylformamide (125 ml) and methanol (20 ml) and the mixture was heated to reflux for 6 days. The reaction mixture was allowed to cool to room temperature and water (200 ml) and ethyl acetate (200 ml) were added. The aqueous layer was extracted with 2 x 200 ml of ethyl acetate, and the combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by chromatography on silica, using a mixture of ethyl acetate and heptane 1:6 as the eluent. Fractions containing the product were evaporated, to afford 180 mg of 3A as an clear oil in 7% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.29 (10H, m); 3.71 (3H, s); 3.62 (4H, s); 3.33-2.51 (7H, m); 1.74 (2H, m). HPLC-MS (Method B): *m/z* = 339 (M+1); *R<sub>t</sub>* = 2.76 min.

Step B: Preparation of (1,4-dibenzyl-[1,4]diazepan-2-yl) -methanol (3B)

20 1,4-Dibenzyl-[1,4]diazepane-2-carboxylic acid methyl ester (3A) (180 mg, 0.53 mmol) was reduced and purified by the method described in example 1, step B, to afford 169 mg of 3B as an yellow oil in 100% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.31 (10H, m); 3.87 (2H, dd); 3.62 (2H, s); 3.43 (2H, d); 3.03-2.43 (7H, m); 1.74 (2H, m). HPLC-MS (Method B): *m/z* = 311 (M+1); *R<sub>t</sub>* = 1.54 min.

25

Step C: Preparation of ([1,4]diazepan-2-yl)methanol. HOAc (3C)

(1,4-Dibenzyl-[1,4]diazepan-2-yl)methanol was hydrogenated for 20 days as described in example 1, step C. The reaction mixture was filtered twice, and the solvents were evaporated. The crude product was crystallized from dry dichloromethane and diethyl ether to afford 62 mg of 3C, as white crystals in 46% yield.

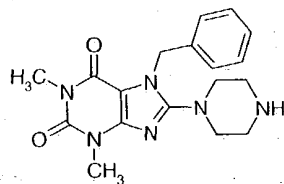
<sup>1</sup>H-NMR (MeOH-d<sub>4</sub>): δ 3.65-2.80 (9H, m); 1.93 (9H, s); 1.27 (2H, m). HPLC-MS (Method B): *m/z* = 131 (M+1); *R<sub>t</sub>* = 0.29 min.

Step D: Preparation of 7-benzyl-8-(3-hydroxymethyl-[1,4]diazepan-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA (3)

5 ([1,4]Diazepan-2-yl)methanol acetate (3C) (62 mg, 0.25 mmol) and 7-benzyl-8-chloro-1,3-dimethyl-3,7-dihydropurine-2,6-dione (50.3 mg, 0.17 mmol) was subjected to micro waves (150°C, 11 bar, 300 W, 12 hours) as described in example 2, step C. The solvents were evaporated and the crude product was purified by preparative HPLC (method A2;  $R_t$  = 6.90 min.) to afford 8 mg of the title compound as a yellow oil in 12% yield. HPLC-MS (Method B):  $m/z$  = 399 (M+1);  $R_t$  = 1.78 min.

10 **Example 4** (General procedure (A))

7-Benzyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA



Step A: Preparation of 7-benzyl-8-chloro-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (4A):

8-Chloro-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (2.0g, 9.3mmol) was dissolved in DMF (50 ml)  $K_2CO_3$  (2.57g, 18.6mmol) and benzyl bromide (1.75g, 10.3 mmol) were added and the reaction mixture was stirred for 15 hours at room temperature. The reaction mixture was evaporated *in vacuo* the residue was dissolved in DCM:H<sub>2</sub>O (1:1) (100 ml) the water phase was extracted with DCM (50ml) the combined organic phase was dried with  $MgSO_4$  filtered and evaporation gave 4A as a white crystalline compound. Yield: 2.92g. Mp: 145.7-147.1°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.2-7.4 (m, 5H); 5.15 (s, 2H); 3.55 (s, 3H); 3.4 (s, 3H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta$  154.8, 151.6; 147.7; 139.1; 135.3; 129.3; 128.9; 128.4; 108.1; 49.6; 30.2; 28.5. HPLC-MS (Method B): M+1= 305;  $R_t$ = 1.9 min.

HPLC (Method D; MeCN: buffer 1:1)  $R_t$ =7.19 min; purity> 99%.

25

Step B: Preparation of 4-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,4,5-tetrahydro-1H-purine-8-yl) -piperazine-1-carboxylic acid tert-butylate (4B):

7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydro-purine-2,6-dione (4A) (1.0 g, 3.3mmol) was dissolved in ethanol (30ml) piperazine-1-carboxylic acid tert-butylate (0.73g, 3.9mmol) and TEA (0.66g, 0.1ml, 6.6mmol) were added and the reaction mixture was heated for 72

30

hours at 120 C° in a sealed vessel. The reaction mixture was evaporated and the remaining oil was purified on a silica gel column using (DCM, MeOH) (39:1) as eluent giving 0.93g of 4B as a yellow oil. Yield: 62%.

HPLC (Method D; MeCN: buffer 1:1)  $R_t$  = 13.15 min; purity > 96%.

5  $R_t$  = 13.15 min. > 96 % purity (Method D: MeCN: buffer (1:1) pH = 3 H<sub>3</sub>PO<sub>4</sub>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.2-7.3 (m, 5H); 5.4 (s, 2H); 3.5 (s, 3H); 3.45 (m, 4H); 3.35 (s, 3H); 3.1 (m, 4H); 1.5 (s, 9H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta$  155.0; 156.4; 151.9; 154.8; 147.8; 136.9; 129.1; 128.8; 128.2; 127.1; 105.3; 80.4; 50.6; 48.9; 43.3 (broad); 30.0; 28.7; 28.1.

10

Step C: Preparation of 4-(7-Benzyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA (4):

4-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,4,5-tetrahydro-1H-purine-8-yl)-piperazine-1-carboxylic acid tert-butylate (4B) (188mg, 0.41mmol) was dissolved in TFA (10ml). The

15 reaction mixture was stirred at room temperature for 2 hours. The mixture was evaporated *in vacuo*. The remaining oil was crystallised from acetone/ether. The title compound was isolated as the white TFA salt 170 mg. Yield: 89%. Mp: 217-19C° decomposes.

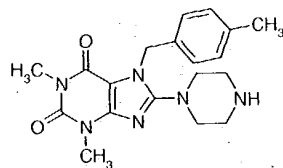
HPLC (Method D; MeCN: buffer 1:1)  $R_t$  = 2.98 min; purity > 99%.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.15-7.4 (m, 5H); 5.4 (s, 2H); 3.45 (s, 3H); 3.4 (broad d, 2H); 3.15

20 (broad d, 2H); 3.05 (s, 3H). HPLC-MS (Method B):  $m/z$  = 355 (M+1);  $R_t$  = 1.699 min; TIC area = 100%

#### Example 5 (General procedure (A))

1,3-Dimethyl-7-(4-methylbenzyl)-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. HCl

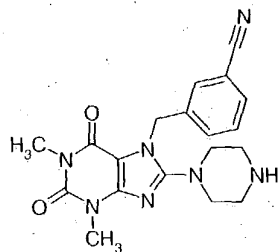


25 HPLC-MS (Method C)  $m/z$  = 369 (M+1);  $R_t$  = 1.319 min.

**Exempl 6** (General procedure (A))

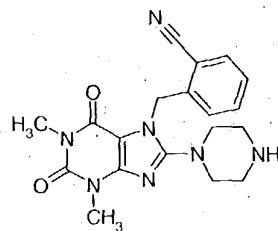
3-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzonitrile.

TFA

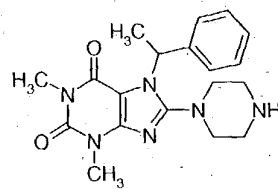
5 HPLC-MS (Method C)  $m/z = 380$  (M+1);  $R_t = 1.22$  min.**Example 7** (General procedure (A))

2-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzonitrile.

TFA

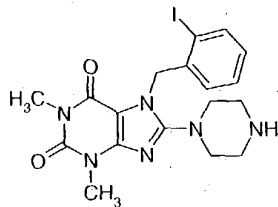
10 HPLC-MS (Method C)  $m/z = 380$  (M+1);  $R_t = 1.18$  min.**Example 8** (General procedure (A))

1,3-Dimethyl-7-(1-phenylethyl)-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z = 369$  (M+1);  $R_t = 2.47$  min

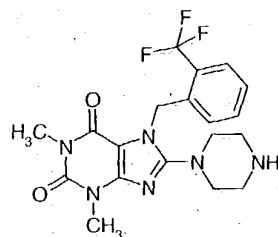
**Example 9** (General procedure (A))

7-(2-Iodobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

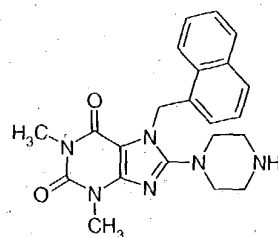
HPLC-MS (Method C)  $m/z$  = 481 (M+1);  $R_t$  = 1.43 min.**5 Example 10** (General procedure (A))

1,3-Dimethyl-8-piperazin-1-yl-7-(2-trifluoromethylbenzyl) -3,7-dihydropurine-2,6-dione.

TFA

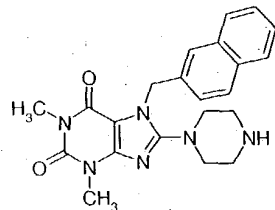
HPLC-MS (Method C)  $m/z$  = 423 (M+1);  $R_t$  = 1.44 min.**10 Example 11** (General procedure (A))

1,3-Dimethyl-7-naphthalen-1-ylmethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

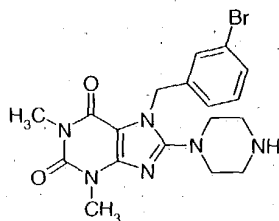
HPLC-MS (Method C)  $m/z$  = 405 (M+1);  $R_t$  = 1.55 min.

**Example 12** (General procedure (A))

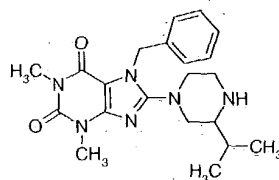
1,3-Dimethyl-7-naphthalen-2-ylmethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z$  = 405 (M+1);  $R_t$  = 1.51 min.**5 Example 13** (General procedure (A))

7-(3-Bromobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z$  = 434 (M+1);  $R_t$  = 1.33 min.**Example 14** (General procedure (A))

10 7-Benzyl-8-(3-isopropylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. HCl

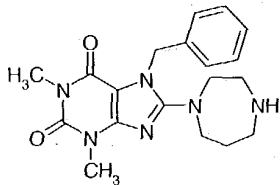


The piperazine moiety was prepared according to the general procedure for preparation of piperazine derivatives.

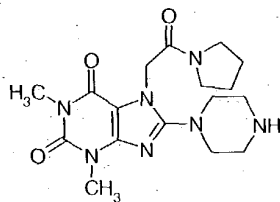
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.1-7.4 (m; 5H); 5.4 (s; 2H); 3.55 (s; 3H); 3.35 (s; 3H); 3.3 (s br; 1H); 2.9-3.05 (m; 3H); 2.65 (t; 1H); 2.45 (dt, 1H); 2.1 (s br; 1H); 1.5 (p; 1H); 0.9 (d; 3H); 0.75 (d; 3H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  157.17; 154.98; 152.12; 148.16; 137.12; 129.15; 128.07; 126.94; 105.33; 60.88; 54.64; 51.04; 49.06; 45.90; 31.42; 30.12; 28.17; 19.21; 19.03.

**Example 15** (General procedure (C))

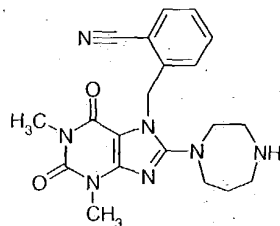
7-Benzyl-8-[1,4]diazepan-1-yl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione. TFA

HPLC-MS (Method B):  $m/z$  = 369;  $R_t$  = 1.75 min. TIC area= 100%**5 Example 16** (General procedure (C))

1,3-Dimethyl-7-(2-oxo-2-pyrrolidin-1-yl-ethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. HCl

HPLC-MS (Method B):  $m/z$  = 376;  $R_t$  = 2.86 min. + 0.47min; Area: 47+53%**10 Example 17** (General procedure (C))

2-(8-[1,4]Diazepan-1-yl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl) - benzonitrile. HCl

Step A

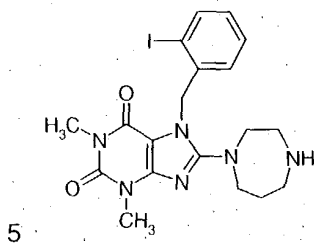
- 15 2-(8-Chloro-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-ylmethyl) benzonitrile (0.5g, 1.5 mmol) and homopiperazine (0.45g, 4.5mmol) and TEA (0.77ml; 7.5 mmol) was heated in 2-propanol in a closed vessel in a micro wave oven at 150°C for 4 hours. The reaction mixture was *evaporated in vacuo*. The remaining oil was purified on a silica gel column with DCM/MeOH (3:1) as eluent, giving the title compound as an oil. The oil was dissolved
- 20 in DCM (3 ml) and hydrochloride in ether was added. Yield 632 mg white crystals. Mp: 160.8-162.3°C.



$^1\text{H-NMR}$  ( $\text{MeOH-}d_4$ ):  $\delta$  7.75 (dd; 1H); 7.65 (dt; 1H); 7.4 (t; 1H); 7.1 (d; 1H); 5.65 (s; 2H); 3.55-3.65 (s; 2H); 3.5 (s; 3H); 3.2 (s; 3H); 3.1 (t; 2H); 2.9 (t; 2H); 1.9 (t,t; 2H).

**Example 18** (General procedure (C))

8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione. HCl

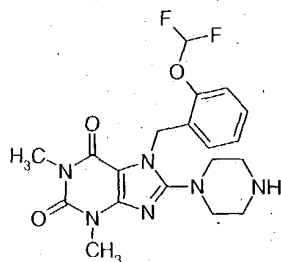


$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.85 (d; 1H); 7.25 (t; 1H); 6.95 (t; 1H); 5.45 (s; 2H); 3.55 (s; 3H); 3.35-3.5 (m; 2H); 3.35 (s; 3H); 2.7-3.1 (m; 6H); 1.75 (m; 2H).

**Example 19** (General procedure (A))

7-(2-Difluoromethoxy-benzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione.

10 TFA

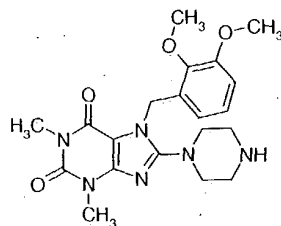


HPLC-MS (Method B):  $m/z$  = 421;  $R_t$  = 3.72 min. area:100%

**Example 20** (General procedure (A))

7-(2,3-Dimethoxy-benzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione.

15 TFA

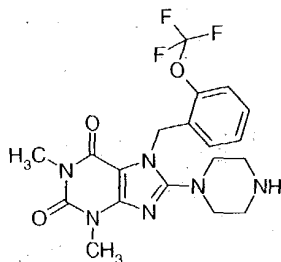


HPLC-MS (Method B):  $m/z$  = 415;  $R_t$  = 3.65 min. area: 100%.

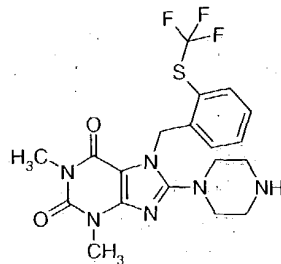
**Example 21** (General procedure (A))

1,3-Dimethyl-8-piperazin-1-yl-7-(2-trifluoromethoxy-benzyl) -3,7-dihydro-purine-2,6-dione.

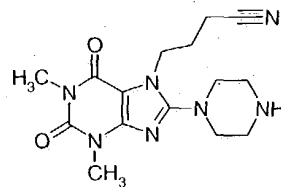
TFA

5 HPLC-MS (Method B):  $m/z$  = 439;  $R_t$  = 2.75min. area 99%**Example 22** (General procedure (A))

1,3-Dimethyl-8-piperazin-1-yl-7-(2-trifluoromethylsulfanyl-benzyl) -3,7-dihydro-purine-2,6-dione. TFA

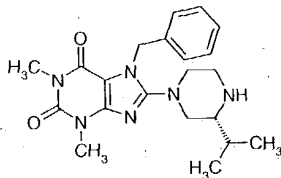
10 HPLC-MS (Method B):  $m/z$  = 455;  $R_t$  = 4.17 min. area 99%**Example 23** (General procedure (A))

4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydro-purin-7-yl) -butyronitrile. TFA

HPLC-MS (Method B):  $m/z$  = 332;  $R_t$  = 2.45 min. area 99,7%

**Example 24** (General procedure (A))

(R) -7-Benzyl-8-(3-isopropylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA

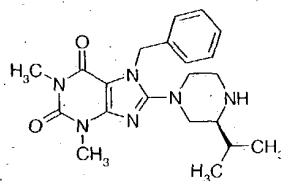


The piperazine moiety was prepared according to the general procedure for preparation of  
5 piperazine derivatives.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.2-7.35 (m; 3H) 7.15 (dd; 2H); 5.4 (s; 2H); 3.6 (s; 3H); 3.35 (s; 3H); 3.3 (m; 5H); 3.1 (m; 2H); 1.8 (p; 1H); 0.9 (d; 3H); 0.75 (d; 3H). HPLC-MS (Method B): *m/z* = 397 (M+1); R<sub>t</sub> = 2.06 min.

**Example 25** (General procedure (A))

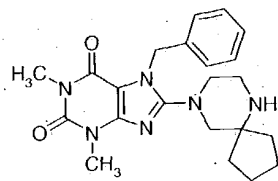
10 (S) -7-Benzyl-8-(3-isopropylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione.  
TFA



<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 11.4 (broad s; 2.5H); 7.25-7.4 (m; 3H); 7.15 (dd; 2H); 5.4 (s; 2H); 3.6 (s; 3H); 3.25-3.5 (m; 7H); 3.0-3.2 (m; 2H); 1.8 (p; 1H); 0.85 (d; 3H); 0.7 (d; 3H). HPLC-MS  
15 (Method B): *m/z* = 397 (M+1); R<sub>t</sub> = 2.09 min.

**Example 26** (General procedure (A))

7-Benzyl-8-(6,9-diazaspiro[4.5]dec-9-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA

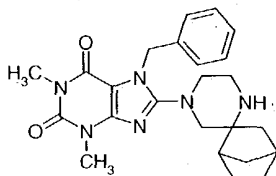


The piperazine moiety was prepared according to the general procedure for preparation of  
20 piperazine derivatives.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 10.0 (broad s; 2H); 8.9 (broad s; 2H); 7.25-7.4 (m; 3H); 7.1 (d; 2H); 5.4 (s; 2H); 3.55 (s; 3H); 3.35-3.4 (m; 5H); 3.1-3.3 (m; 4H); 1.6-1.85 (m; 6H); 1.3 (m; 2H).  
HPLC-MS (Method B): *m/z* = 409 (M+1); R<sub>t</sub> = 2.11 min.

**Example 27** (General procedure (A))

7-Benzyl-8-(piperazin-3-spiro-3'-bicyclo[2,2,1]heptane-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione. TFA



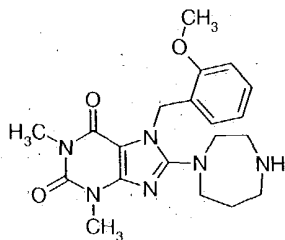
- 5 The piperazine moiety was prepared according to the general procedure for preparation of piperazine derivatives.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 11.1 (broad s; 1H); 8.9 (broad s; 1H); 7.25-7.4 (m; 3H); 7.1 (dd; 2H); 5.45 (s; 2H); 3.5 (s; 3H); 3.15-3.4 (m; 9H); 2.2-2.3 (d; 2H); 1.1-1.6 (m; 7H); 0.9 (d; 1H).  
HPLC-MS (Method B): *m/z* = 435 (M+1); *R*<sub>t</sub> = 2.34 min.

10

**Example 28** (General procedure (A))

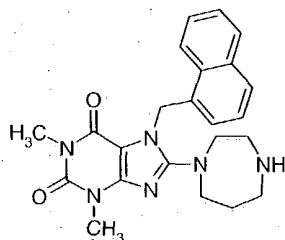
8-[1,4]Diazepan-1-yl-7-(2-methoxy-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione. TFA



- 15 HPLC-MS (Method B): *m/z* = 399; *R*<sub>t</sub> = 1.93 min. UV area=98.63%

**Example 29** (General procedure (A))

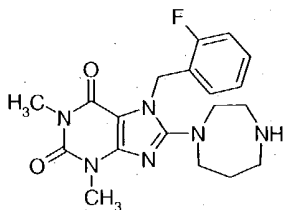
8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-naphthalen-1-ylmethyl-3,7-dihydro-purine-2,6-dione. TFA



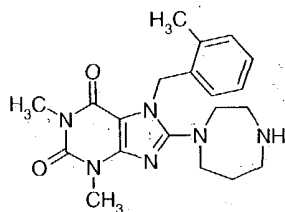
- 20 HPLC-MS (Method B): *m/z* = 419; *R*<sub>t</sub> = 2.26 min. UVarea= 99.7%.

**Example 30** (General procedure (A))

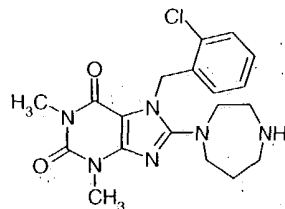
8-[1,4]Diazepan-1-yl-7-(2-fluoro-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione. TFA

HPLC-MS (Method B):  $m/z$  = 387;  $R_t$  = 1.86 min. UVarea= 94.4%.**5 Example 31** (General procedure (A))

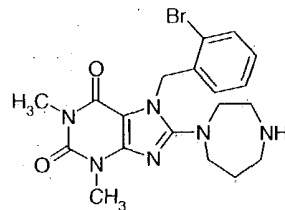
8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-methyl-benzyl) -3,7-dihydro-purine-2,6-dione. TFA

HPLC-MS (Method B):  $m/z$  = 383 (M+1);  $R_t$  = 1.99 min. UVarea=97.68%.**Example 32** (General procedure (A))

10 7-(2-Chloro-benzyl) -8-[1,4]diazepan-1-yl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione. TFA

HPLC-MS (Method B):  $m/z$  = 403; 405; 406; (M+1);  $R_t$  = 1.97 min. UVarea= 98.93.**Example 33** (General procedure (A))

7-(2-Bromo-benzyl) -8-[1,4]diazepan-1-yl-1,3-dimethyl-3,7-dihydro-purine-2,6-dione. TFA

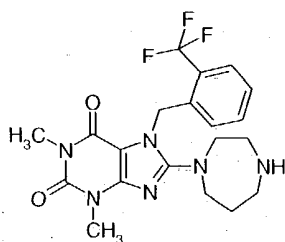


15

HPLC-MS (Method B):  $m/z$  = 447; 450; (M+1);  $R_t$  = 2.09 min. UVarea= 98.51.

**Example 34** (General procedure (A))

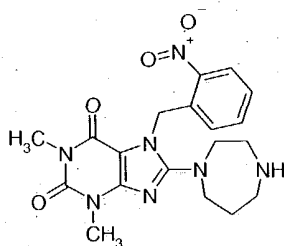
8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-trifluoromethyl-benzyl) -3,7-dihydro-purine-2,6-dione. TFA



5 HPLC-MS (Method B):  $m/z$  = 437 ( $M+1$ );  $R_t$  = 2.20 min. UVarea=99.50%.

**Example 35** (General procedure (A))

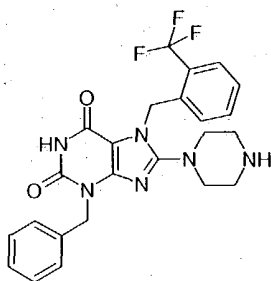
8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-nitro-benzyl) -3,7-dihydro-purine-2,6-dione. HCl



HPLC-MS (Method B):  $m/z$  = 437 ( $M+23$ );  $R_t$  = 2.23 min. UV area= 100%.

**10 Example 36** (General procedure (B))

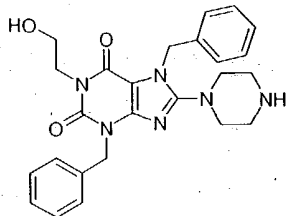
3-Benzyl-8-piperazin-1-yl-7-(2-trifluoromethyl-benzyl) -3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  11,12 (s, 1H); 8,83 (s, 1H); 7,86-7,71 (d, 2H); 7,71-7,45 (m, 2H); 7,45-7,23 (m, 5 H); 7,08-6,98 (d, 1 H); 5,48 (s, 1H); 5,10 (s, 1H); 3,34-3,01 (m, 4H)

**Example 37** (General procedure (B))

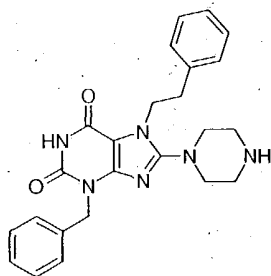
3,7-Dibenzyl-1-(2-hydroxy-ethyl)-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 8.86 (s br, 2H); 7.40-7.18 (m, 10H); 5.41 (s, 2H); 5.13 (s, 2H); 3.93  
5 (t, 2H); 3.45 (t, 2H); 3.31 (s br, 4H); 3.19 (s br, 4H).

**Example 38** (General procedure (B))

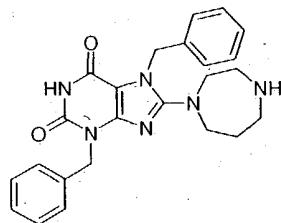
3-Benzyl-7-phenethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 11.11 (s, 1H); 8.79 (s br, 2H); 7.40-7.05 (m, 10H); 5.02 (s, 2H);  
10 4.30 (t, 2H); 3.09 (s br, 8H); 3.03 (t, 2H).

**Example 39** (General procedure (B))

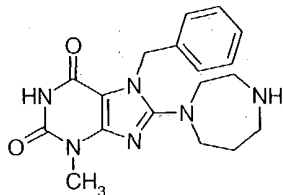
3,7-Dibenzyl-8-[1,4]diazepan-1-yl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.67-6.92 (m, 10H); 5.42 (s, 2H); 5.04 (s, 2H); 3.89-3.35 (m, 5H);  
15 2.96-2.35 (m, 5H); 1.68 (s, 2H). HPLC-MS *m/z* = 431

**Example 40** (General procedure (B))

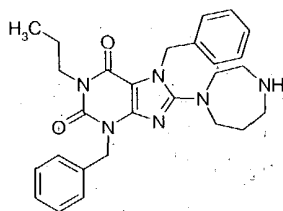
7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.89 (s, 1H); 9.19 (s, 2H); 7.46-7.00 (m, 5H) 5.42 (s, 2H) 3.67 (s br, 2H); 3.53-3.40 (m, 2H); 3.32 (s, 3H); 3.23 (s br, 2H); 3.14 (s, 2H); 2.00 (m, 2H) HPLC-MS  $m/z \approx 355$

**Example 41** (General procedure (B))

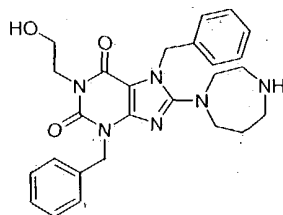
3,7-Dibenzyl-8-[1,4]diazepan-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



10  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.67 (s br, 2H); 7.45-7.06 (m, 10H); 5.46 (s, 2H) 5.12 (s, 2H) 3.79 (t, 2H); 3.67 (m, 2H); 3.50 (m, 2H); 3.27 (s br, 2H) 3.16 (s br, 2H); 1.98 (m, 2H); 1.52 (m, 2H); 0.81 (t, 3H).

**Example 42** (General procedure (B))

3,7-Dibenzyl-8-[1,4]diazepan-1-yl-1-(2-hydroxy-ethyl) -3,7-dihydro-purine-2,6-dione. TFA

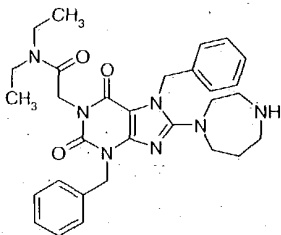


15  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.79 (s, 2H); 7.41- 7.22 (m, 8H); 7.20- 7.07 (m, 2H); 5.47 (s, 2H); 5.12 (s, 2H); 4.00-3.86 (t, 2H); 3.73-3.61 (m, 2 H); 3.54-3.40 (m, 4H) 3.27 (s, 2H); 3,15 (s, 2H) 1.98 (s, 2H)



**Example 43** (General procedure (B))

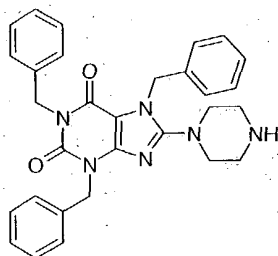
2-(3,7-Dibenzyl-8-[1,4]diazepan-1-yl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl) -*N,N*-diethyl-acetamide



- 5  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.67 (s br, 2H); 7.41-7.20 (m, 8H); 7.16-7.03 (m, 2H); 5.47 (s, 2H); 5.13 (s, 2H); 4.64 (s, 2H); 3.69 (s br, 2H); 3.51 (t, 2H) 3.44-3.10 (m, 7H); 2.67 (s, 1H); 1.98 (s br, 2H); 1.16 (t, 3H) 0.99 (t, 3H)

**Example 44** (General procedure (B))

1,3,7-Tribenzyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA

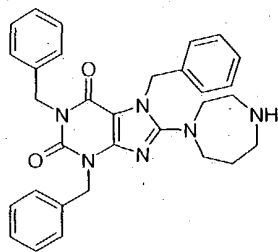


10

- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.83 (s br, 2H); 7.48-7.16 (m, 15H); 5.40 (s, 2H); 5.14 (s, 2H); 5.02 (s, 2H); 3.20 (s br, 4H).

**Example 45** (General procedure (B))

1,3,7-Tribenzyl-8-[1,4]diazepan-1-yl-3,7-dihydro-purine-2,6-dione. TFA

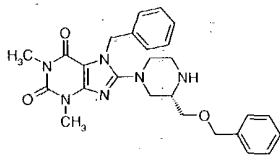


15

- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.76 (s br, 2H); 7.58-7.04 (m, 15H); 5.48 (s, 2H) 5.13 (s, 2H); 5.03 (s, 2H); 3.70 (s br, 2H); 3.52 (t, 2H); 3.29 (s br, 2H); 3.17 (s br, 2H); 1.99 (s br, 2H)

**Example 46** (General procedure (A))

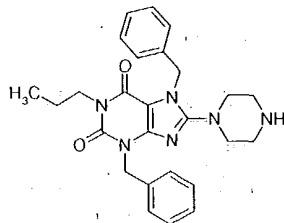
(S) -7-Benzyl-8-(3-benzoyloxymethylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione



- 5 The piperazine moiety was prepared according to the general procedure for preparation of piperazine derivatives.
- <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.1-7.45 (m; 5H); 5.35 (s br; 2H); 4.5 (s; 2H); 3.5 (s; 3H); 3.35 (s; 3H); 3.2-3.0 (m; 3H); 2.7-3.1 (m; 5H); 2.25 (s br; 1H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 156.92; 155.07; 152.11; 148.12; 138.22; 137.08; 129.16; 128.85; 128.22; 128.19; 128.15; 127.21; 105.35; 73.89; 72.07; 54.65; 53.89; 53.30; 51.41; 49.11; 45.14; 30.14; 28.22.

**Example 47** (General procedure (B))

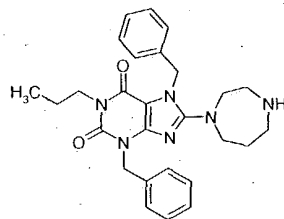
3,7-Dibenzyl-8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



- <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 8.95 (s br, 2H); 7.40-7.20 m, 10 H); 5.40 (s, 2H); 5.13 (s, 2H); 3.79 (t, 2H); 3.32 (m, 4H); 3.20 (m, 4H); 1.50 (sextet, 2H); 0.81 (t, 3H). HPLC-MS (Method C): *m/z* = 459 (M+1); *R*<sub>t</sub> = 4.62 min

**Example 48** (General procedure (B))

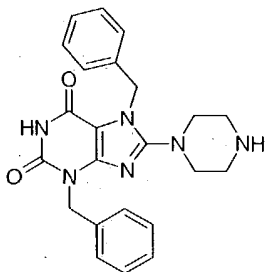
3,7-Dibenzyl-8-[1,4]diazepan-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



- 20 HPLC-MS (Method C): *m/z* = 473 (M+1); *R*<sub>t</sub> = 4.72 min

**Example 49** (General procedure (B))

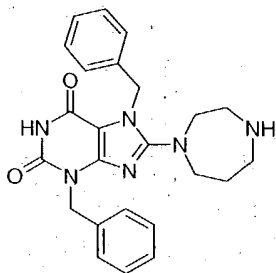
3,7-Dibenzyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  11.05 (s, 1H); 8.72 (s, br 2H); 7.40-7.20 (m, 10H); 5.37 (s, 2H);  
 5 5.07 (s, 2H). HPLC-MS (Method C): *m/z* = 417 (M+1); *R*<sub>t</sub> = 3.69 min

**Example 50** (General procedure (B))

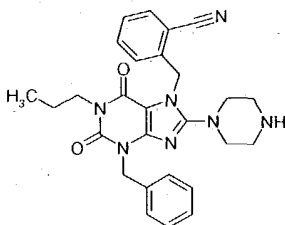
3,7-Dibenzyl-8-[1,4]diazepan-1-yl-3,7-dihydro-purine-2,6-dione. TFA



DMSO *d*<sub>6</sub>  $\delta$  10.90 (s, 1H); 8.65 (s br, 2H); 7.40-7.20 (m, 8H); 7.14 (d, 2H); 5.43 (s, 2H);  
 10 5.06 (s, 2H); 3.65 (m, 2H); 3.48 (m, 2H); 3.26 (m, 2H); 3.16 (s br, 2H); 1.97 (m, 2H)  
 HPLC-MS (Method C): *m/z* = 431 (M+1); *R*<sub>t</sub> = 3.83 min

**Example 51** (General procedure (B))

2-(3-Benzyl-2,6-dioxo-8-piperazin-1-yl-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) - benzonitrile

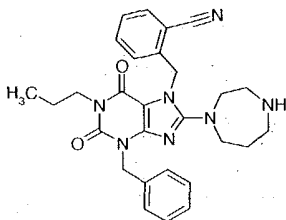


15

<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.73 (s br, 2H); 7.88 (d, 1H); 7.64 (t, 1H); 7.49 (t, 1H); 7.42-7.25  
 (m, 5H); 7.15 (d, 1H); 5.56 (s, 2H); 3.73 (t, 2H); 1.46 (q, 2H); 0.77 (t, 3H). HPLC-MS  
 (Method C): *m/z* = 484 (M+1); *R*<sub>t</sub> = 4.56 min

**Example 52** (General procedure (B))

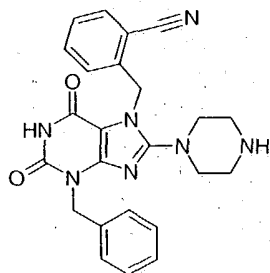
2-(3-Benzyl-8-[1,4]diazepan-1-yl-2,6-dioxo-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) - benzonitrile



- 5  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.66 (s br, 2H); 7.89 (d, 1H); 7.65 (t, 1H); 7.52 (t, 1H); 7.42-7.10 (m, 5H); 7.12 (d, 1H); 5.59 (s, 2H); 5.14 (s, 2H); 3.78-3.65 (m, 4H); 3.48 (t, 2H); 3.31 (s br, 2H); 3.19 (s br, 2H); 2.00 (m 2H); 1.45 (q, 2H); 0.77 (t, 3H).

**Example 53** (General procedure (B))

2-(3-Benzyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydro-purin-7-ylmethyl) - benzonitrile



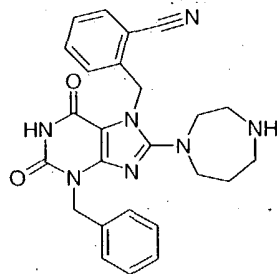
10

- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  11.02 (s, 1H); 8.73 (s br 2H); 7.88 (d, 1H); 7.66 (t, 1H); 7.50 (t, 1H); 7.40-7.25 (m, 5H); 7.16 (d, 1H); 5.53 (s, 2H); 5.08 (s, 2H); 3.38 (s br, 4H); 3.20 (s br, 4H)

**Example 54** (General procedure (B))

2-(3-Benzyl-8-[1,4]diazepan-1-yl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl) -

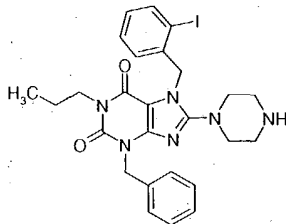
15 benzonitrile



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  10.90 (s, 1H); 8.67 (s br, 1H); 7.89 (d, 1H); 7.67 (t, 1H); 7.51 (t, 1H); 7.44-7.25 (m, 5H); 7.12 (d, 1H); 5.56 (s, 2H); 5.07 (s, 2H); 3.68 (m, 2H); 3.46 (m, 2H); 3.36 (s br, 2H); 3.19 (s br, 2H); 1.89 (m, 2H).

**Example 55** (General procedure (B))

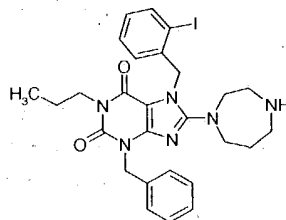
- 5 3-Benzyl-7-(2-iodo-benzyl) -8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.71 (s br, 2H); 7.93 (d 1H); 7.42-7.25 (m, 6H); 7.09 (d, 1H); 6.8 (d, 1H); 5.28 (s, 2H); 5.17 (s, 2H); 3.75 (t, 2H); 3.16 (s br 4H); 1.48 (q, 2H); 0.79 (t, 3H).

**Example 56** (General procedure (B))

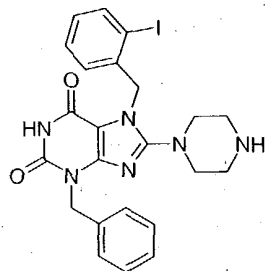
- 10 3-Benzyl-8-[1,4]diazepan-1-yl-7-(2-iodo-benzyl) -1-propyl-3,7-dihydro-purine-2,6-dione. TFA



- <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.64 (s br, 2H); 7.93 (d, 1H); 7.44-7.25 (m, 6H); 7.09 (t, 1H); 6.76 (d, 1H); 5.29 (s, 2H); 5.16 (s, 2H); 3.75 (t, 2H); 3.67 (m, 2H); 3.41 (m, 2H); 3.16 (m, 2H); 1.95 (m, 2H); 1.49 (q, 2H); 0.80 (t, 3H). HPLC-MS (Method C): *m/z* = 599 (*M*+1); *R*<sub>t</sub> = 4.96 min

**Example 57** (General procedure (B))

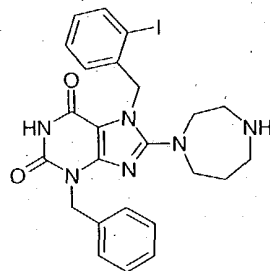
3-Benzyl-7-(2-iodo-benzyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  11.03 (s, 1H); 8.71 (s br, 1H); 7.92 (d, 1H); 7.42-7.28 (m, 6H); 7.08 (d, 1H); 6.81 (d, 1H); 5.26 (s, 2H); 5.10 (s, 2H); 3.15 (s br 4H).

**Example 58** (General procedure (B))

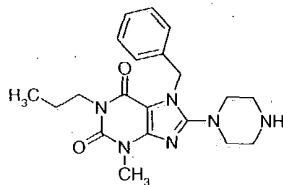
3-Benzyl-8-[1,4]diazepan-1-yl-7-(2-iodo-benzyl) -3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.91 (s, 1H); 8.64 (s br, 2H); 7.93 (d, 1H); 7.44-2.25 (m, 6H); 7.09 (d, 1H); 6.75 (d, 1H); 5.27 (s, 2H); 5.09 (s, 2H); 3.65 (m, 2H); 3.39 (m, 1H); 3.30-3.22 (m, 3H); 3.15 (s br 2H); 1.94 (m, 2H).

**Example 59**

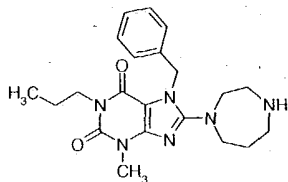
7-Benzyl-3-methyl-8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.77 (s br 2H); 7.37-7.25 (m, 3H); 7.21 (d, 2H); 5.40 (s, 2H); 3.80 (t, 2H); 3.21 (s br 4H); 1.53 (q, 2H); 0.83 (t, 3H).

**Example 60** (General procedure (B))

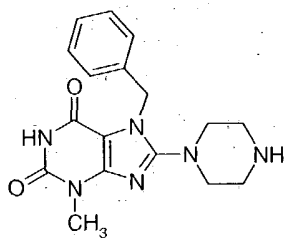
7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.66 (s br, 2H); 7.40-7.25 (m, 3H); 7.12 (d, 2H); 5.46 (s, 2H); 3.80 (t, 2H); 3.66 (m, 2H); 3.50 (m, 2H); 3.28 (m, 2H); 3.17 (s br, 2H); 1.99 (m, 2H); 1.53 (q, 2H); 0.83 (t, 3H).

**Example 61** (General procedure (B))

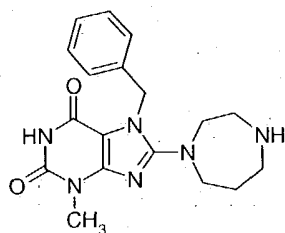
7-Benzyl-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.97 (s, 1H); 8.66 (s br) 7.40-7.25 (m, 3H); 7.21 (d, 2H); 5.37 (s, 2H).

**Example 62** (General procedure (B))

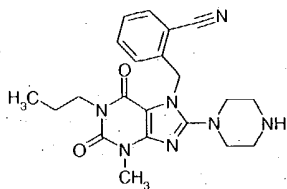
7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.84 (s, 1H); 8.61 (s br 2H); 7.40-7.25 (m, 3H); 7.13 (d, 2H); 5.43 (s, 2H); 3.65 (m, 2H); 3.47 (m, 2H); 3.17 (m, 2H); 1.98 (m, 2H).

**Example 63** (General procedure (B))

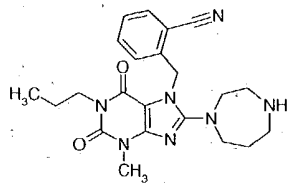
2-(3-Methyl-2,6-dioxo-8-piperazin-1-yl-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) - benzonitrile



- 5  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.78 (s br 2H); 7.88 (d, 1H); 7.63 (t, 1H); 7.49 (t, 1H); 7.08 (d, 1H); 5.55 (s, 2H); 3.73 (t, 2H); 3.22 (s br, 4H); 1.47 (q, 2H); 0.78 (t, 3H).

**Example 64** (General procedure (B))

2-(8-[1,4]Diazepan-1-yl-3-methyl-2,6-dioxo-1-propyl-1,2,3,6-tetrahydro-purin-7-ylmethyl) - benzonitrile

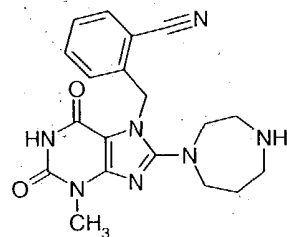


10

- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.66 (s br, 2H); 7.89 (d, 1H); 7.65 (t, 1H); 7.50 (t, 1H); 7.06 (d, 1H); 5.58 (s, 2H); 3.73 (t, 2H); 3.69 (m, 2H); 3.47 (m, 2H); 3.42 (s, 3H); 3.21 (m, 2H); 2.00 (m, 2H); 1.48 (sextet, 2H); 0.78 (t, 3H).

**Example 65** (General procedure (B))

- 15 2-(8-[1,4]Diazepan-1-yl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl) - benzonitrile

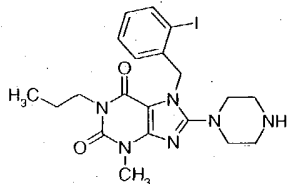


- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  10.84 (s, 1H); 8.94 (s br, 1H); 8.69 (s br, 1H); 7.89 (d, 1H); 7.66 (t, 1H); 7.50 (t, 1H); 7.06 (d, 1H); 5.56 (s, 2H); 3.68 (m, 2H); 3.46 (m, 2H); 3.42 (s, 3H).



**Example 66** (General procedure (B))

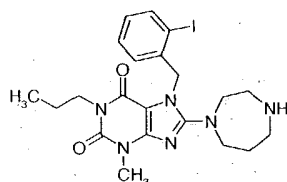
7-(2-Iodo-benzyl) -3-methyl-8-piperazin-1-yl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.73 (s br, 2H); 7.92 (d, 1H); 7.33 (t, 1H); 7.07 (t, 1H); 6.70 (d, 1H);  
 5.28 (s, 2H); 3.75 (t, 2H); 3.44 (s, 3H); 3.17 (s br, 4H); 1.49 (sextet, 2H); 0.80 (t, 3H).

**Example 67** (General procedure (B))

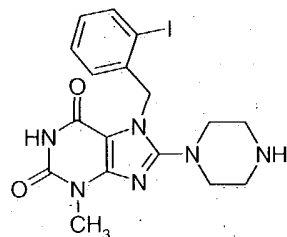
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -3-methyl-1-propyl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.66 (s br, 2H); 7.93 (d, 1H); 7.35 (t, 1H); 7.08 (t, 1H); 6.69 (d, 1H);  
 5.30 (s, 2H); 3.75 (t, 2H); 3.43 (s, 3H); 3.28 (m, 2H); 3.17 (m, 2H); 1.95 (m, 2H); 1.50  
 (sextet, 2H); 0.81 (t, 3H).

**Example 68** (General procedure (B))

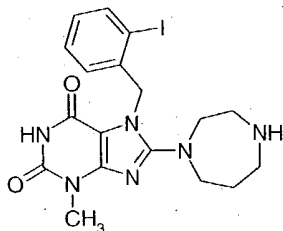
7-(2-Iodo-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  10.96 (s, 1H); 8.72 (s br); 7.72 (d, 1H); 7.34 (t, 1H); 7.07 (t, 1H);  
 6.73 (d, 1H); 5.26 (s, 2H); 3.15 (m, 4H).

**Example 69** (General procedure (B))

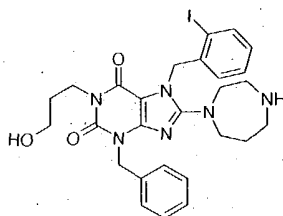
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  10.84 (s, 1H); 8.62 (s br, 2H); 7.93 (d, 1H); 7.36 (t, 1H); 7.08 (t, 1H); 6.69 (d, 1H); 5.28 (s, 2H); 3.65 (dm, 2H); 3.39 (m, 2H); 3.36 (s, 3H); 3.16 (m, 2H); 1.94 (m, 2H).

**Example 70** (General procedure (B))

3-Benzyl-8-[1,4]diazepan-1-yl-1-(3-hydroxy-propyl) -7-(2-iodo-benzyl) -3,7-dihydro-purine-2,6-dione. TFA

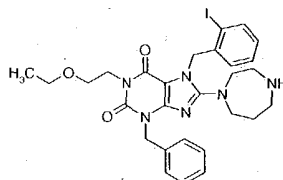


10

<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  (Selected peaks) 8.62 (s br, 2H); 7.88 (d, 1H); 7.40-7.20 (m, 7H); 7.04 (t, 1H); 6.71 (d, 1H); 5.23 (s, 2H); 5.10 (s, 2H);

**Example 71** (General procedure (B))

3-Benzyl-8-[1,4]diazepan-1-yl-1-(2-ethoxy-ethyl) -7-(2-iodo-benzyl) -3,7-dihydro-purine-2,6-dione. TFA

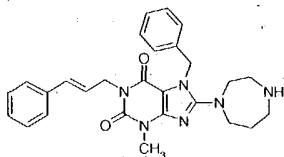


<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  (Selected peaks) 8.62 (s br, 2H); 7.88 (d, 1H); 7.40-7.20 (m, 7H); 7.04 (t, 1H); 6.71 (d, 1H); 5.24 (s, 2H); 5.101 (s, 2H); 0.93 (t, 3H).

**Example 72** (General procedure (B))

7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(3-phenyl-allyl) -3,7-dihydro-purine-2,6-dione.

TFA

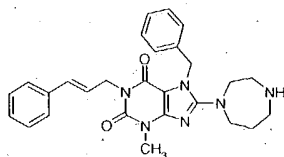


- 5  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.66 (s br, 2H); 7.50-7.20 (m) 7.14 (d, 2H); 6.46 (d, 1H); 6.27 (dt, 1H); 5.47 (s, 2H); 4.61 (d, 2H); 3.67 (m, 2H); 3.50 (m, 2H); 3.43 (s, 3H); 3.17 (m, 2H); 2.00 (m, 2H).

**Example 73** (General procedure (B))

7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(3-phenylallyl) -3,7-dihydropurine-2,6-dione.

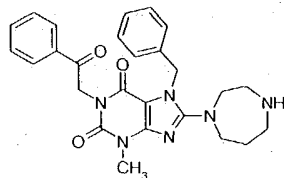
10 TFA



- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.66 (s br, 2H); 7.50-7.20 (m) 7.14 (d, 2H); 6.46 (d, 1H); 6.27 (dt, 1H); 5.47 (s, 2H); 4.61 (d, 2H); 3.67 (m, 2H); 3.50 (m, 2H); 3.43 (s, 3H); 3.17 (m, 2H); 2.00 (m, 2H).

15 **Example 74** (General procedure (B))

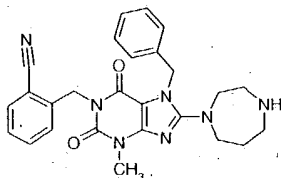
7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(2-oxo-2-phenyl-ethyl) -3,7-dihydro-purine-2,6-dione. TFA



- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.62 (s br, 2H); 8.05 (d, 2H); 7.71 (t, 1H); 7.58 (t, 2H); 7.40-7.25 (m, 3H); 7.13 (d, 3H) 5.46 (s, 2H); 5.35 (s, 2H); 3.71 (m, 2H); 3.53 (m, 2H); 3.44 (s, 3H); 3-20 (m, 2H); 2.01 (m, 2H).

**Example 75** (General procedure (B))

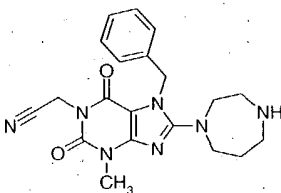
2-(7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-ylmethyl) - benzonitrile



- 5  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.66 (s br, 2H); 7.81 (d, 1H); 7.61 (t, 1H); 7.44 (t, 1H); 7.40-7.25 (m, 3H); 7.18 (d, 1H); 7.14 (d, 2H); 5.46 (s, 2H); 5.21 (s, 2H); 3.69 (m, 2H); 3.52 (m, 2H); 3.42 (s, 3H); 3.20 (m, 2H); 2.00 (m, 2H).

**Example 76** (General procedure (B))

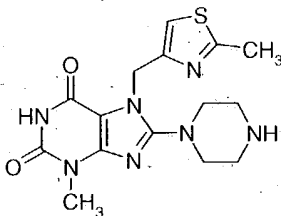
(7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-purin-1-yl) -  
10 acetonitrile



- $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.66 (s br, 2H); 7.40-7.25 (m, 3H); 5.46 (s, 2H); 4.84 (s, 2H); 3.69 (m, 2H); 3.52 (m, 2H); 3.44 (s, 3H); 3.17 (m, 2H); 1.99 (m, 2H).

**Example 77** (General procedure (B))

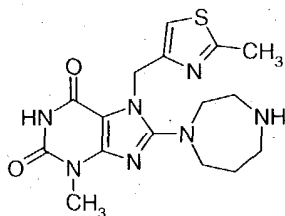
15 3-Methyl-7-(2-methyl-thiazol-4-ylmethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione.  
TFA



- $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.99 (s, 1H); 8.88 (s br, 2H); 7.31 (s, 1H); 5.36 (s, 2H); 3.42 (m, 4H); 3.32 (s, 3H); 3.22 (s br, 4H); 2.60 (s, 3H)

**Example 78** (General procedure (B))

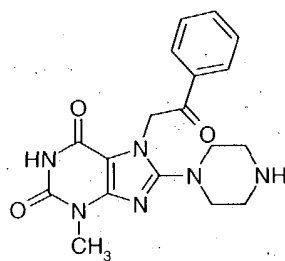
8-[1,4]Diazepan-1-yl-3-methyl-7-(2-methyl-thiazol-4-ylmethyl) -3,7-dihydro-purine-2,6-dione. TFA



- 5  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.87 (s, 1H); 8.88 (s br, 2H); 7.21 (s, 1H); 5.41 (s, 2H); 3.73 (m, 2H); 3.57 (t, 2H); 3.31 (s br, 4H); 3.23 (s br, 2H); 2.61 (s, 3H); 2.51 (m, 1H); 2.04 (m, 2H); HPLC-MS  $m/z$  = 376

**Example 79** (General procedure (B))

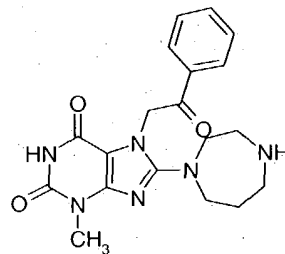
3-Methyl-7-(2-oxo-2-phenyl-ethyl) -8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



- 10  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  11.00 (s, 1H); 9.89 (s br, 2H); 8.07 (d, 2H); 7.74 (t, 1H); 7.64 (t, 2H); 5.75 (s, 2H); 3.36 (s, 3H); 3.29 (m, 4H); 3.24 (m, 4H). HPLC-MS  $m/z$  = 369

**Example 80** (General procedure (B))

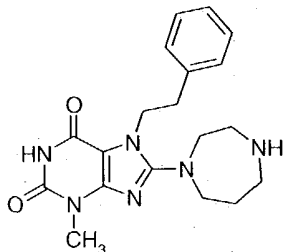
8-[1,4]Diazepan-1-yl-3-methyl-7-(2-oxo-2-phenyl-ethyl) -3,7-dihydro-purine-2,6-dione. TFA



- 15  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.88 (s, 1H); 8.87 (s br, 2H); 8.09-7.60 (m, 5H); 5.80 (s, 2H); 3.67 (t, 2H); 3.46 (t, 2H); 3.34 (s, 3H); 3.21 (t, 2H); 2.01 (m, 2H). HPLC-MS  $m/z$  = 383

**Example 81** (General procedure (B))

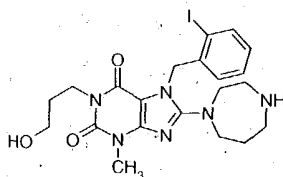
8-[1,4]Diazepan-1-yl-3-methyl-7-phenethyl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  10.89 (s, 1H); 8.87 (s br, 2H); 7.29-7.12 (m, 5H); 4.29 (t, 2H); 3.54 (m, 2H); 3.42 (t, 2H); 3.28 (s, 3H); 3.21 (s br, 2H); 3.00 (t, 2H) 2.03 (m, 2H). HPLC-MS *m/z* = 369.

**Example 82** (General procedure (B))

8-[1,4]Diazepan-1-yl-1-(3-hydroxy-propyl) -7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione. TFA

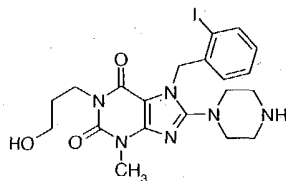


10

<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.72 (s br, 2H); 7.93 (d, 1H); 7.35 (t, 1H); 7.08 (t, 1H); 6.70 (d, 1H); 5.29 (s, 2H); 3.84 (t, 2H); 3.66 (m, 2H); 3.43 (s, 3H); 3.42-3.33 (m, 4H) 3.27 (m, 2H); 3.15 (m, 2H); 1.94 (m, 2H); 1.62 (q, 2H); HPLC-MS (Method C): *m/z* = 539 (M+1); *R*<sub>t</sub> = 3.69 min

**Example 83** (General procedure (B))

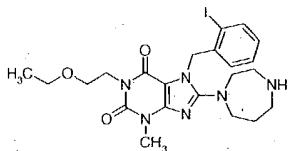
1-(3-Hydroxy-propyl) -7-(2-iodo-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  8.80 (s br 2H); 7.92 (d, 1H); 7.33 (t, 1H); 7.07 (t, 1H); 6.71 (d, 1H); 5.27 (s, 2H); 3.83 (t, 2H); 3.44 (s, 3H); 3.37 (t, 2H); 3.29 (m, 2H); 3.16 (m, 2H); 1.62 (q, 2H); HPLC-MS (Method C): *m/z* = 525 (M+1); *R*<sub>t</sub> = 3.53 min

**Example 84** (General procedure (B))

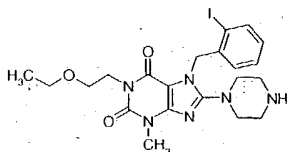
8-[1,4]Diazepan-1-yl-1-(2-ethoxy-ethyl) -7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione. TFA



5  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.64 (s br 2H); 7.93 (d, 1H); 7.35 (t, 1H); 7.08 (t, 1H); 6.69 (d, 1H); 5.28 (s, 2H); 3.96 (t, 2H); 3.66 (m, 2H); 3.16 (m, 2H); 3.43 (s, 3H); 1.01 (t, 3H). HPLC-MS (Method C):  $m/z$  = 553 ( $\text{M}+1$ );  $R_t$  = 4.09 min

**Example 85** (General procedure (B))

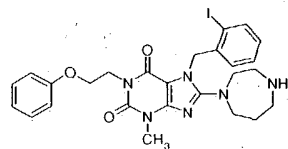
10 1-(2-Ethoxy-ethyl) -7-(2-iodo-benzyl) -3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.80 (s br, 2H); 7.92 (d, 1H); 7.32 (t, 1H); 7.07 (t, 1H); 6.70 (d, 1H); 5.27 (s, 2H); 3.96 (t, 1H); 3.48-3.40 (m, 5H); 3.38 (q, 2H); 3.30 (m, 4H); 3.16 (m, 4H); 1.00 (t, 3H). HPLC-MS (Method C):  $m/z$  = 539 ( $\text{M}+1$ );  $R_t$  = 4.03 min

15 **Example 86** (General procedure (B))

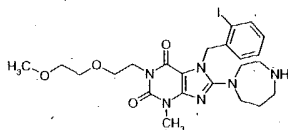
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -3-methyl-1-(2-phenoxy-ethyl) -3,7-dihydro-purine-2,6-dione. TFA



HPLC-MS (Method C):  $m/z$  = 601 ( $\text{M}+1$ );  $R_t$  = 4.73 min

**Example 87** (General procedure (B))

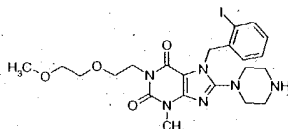
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -1-[2-(2-methoxy-ethoxy) -ethyl]-3-methyl-3,7-dihydro-purine-2,6-dione. TFA



- 5  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.70 (s br, 2H); 7.93 (d, 1H); 7.35 (t, 1H); 7.08 (t, 1H); 6.70 (d, 1H); 5.29 (s, 2H); 3.96 (t, 2H); 3.66 (m, 2H); (3.52-3.44 (m, 4H); 3.43 (s, 3H); 3.42-3.37 (m, 2H); 3.36-3.31 (m, 2H); 3.26 (m, 2H); 3.20 (m, 5H); 1.94 (m, 2H). HPLC-MS (Method C):  $m/z = 583$  ( $M+1$ );  $R_t = 3.96$  min

**Example 88** (General procedure (B))

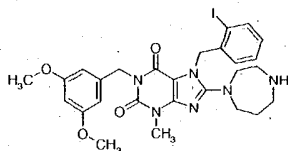
- 10 7-(2-Iodo-benzyl) -1-[2-(2-methoxy-ethoxy) -ethyl]-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA



- $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.78 (s br, 2H); 7.93 (d, 1H); 7.33 (t, 1H); 7.07 (t, 1H); 6.70 (t, 1H); 5.27 (s, 2H); 3.96 (t, 2H); 3.52-3.42 (m, 4); 3.44 (s, 3H); 3.38-3.27 (m, 6H); 3.20-3.12 (m, 4H) 3.18 (s, 3H). HPLC-MS (Method C):  $m/z = 569$  ( $M+1$ );  $R_t = 3.86$  min

**Example 89** (General procedure (B))

8-[1,4]Diazepan-1-yl-1-(3,5-dimethoxy-benzyl) -7-(2-iodo-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione. TFA

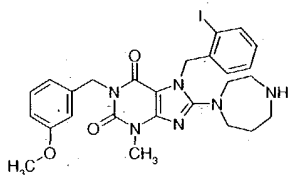


- 20  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  8.70 (s br, 2H); 7.91 (d, 1H); 7.34 (t, 1H); 7.07 (t, 1H); 6.74 (d, 1H); 6.34 (m, 1H); 6.32 (m, 2H); 5.30 (s, 2H); 4.91 (s, 2H); 3.69 (m, 2H); 3.66 (s, 6H); 3.44 (s, 3H); 3.42 (m, 2H); 3.28 (m, 2H); 3.17 (m, 2H); 1.95 (m, 2H). HPLC-MS (Method C):  $m/z = 631$  ( $M+1$ );  $R_t = 4.72$  min



**Example 90** (General procedure (B))

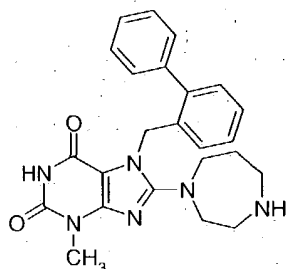
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl) -1-(3-methoxy-benzyl) -3-methyl-3,7-dihydro-purine-2,6-dione. TFA



- 5  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  8.70 (s br, 2H); 7.93 (d, 1H); 7.35 (t, 1H); 7.18 (t, 1H); 7.08 (t, 1H); 6.80-6.70 (m, 4H); 5.30 (s, 2H); 4.95 (s, 2H); 3.68 (s, 3H); 3.44 (s, 3H); 3.42 (m, 2H); 3.28 (m, 2H); 3.16 (m, 2H); 1.95 (m, 2H). HPLC-MS (Method C):  $m/z$  = 601 ( $\text{M}+1$ );  $R_t$  = 4.62 min

**Example 91** (General procedure (B))

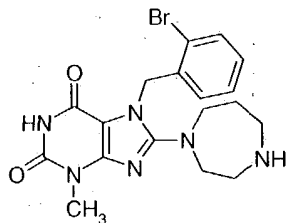
10 7-Biphenyl-2-ylmethyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione. TFA



- $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.81 (s, 1H); 8.74 (s br, 2H); 7.5-7.22 (m, 9H); 5.35 (s, 2H); 5.53 (t, 2H); 3.29 (s, 3H); 3.26 (m, 2H); 3.15 (s br, 2H); 3.06 (s br, 2H); 1.82 (m, 2H) HPLC-MS  $m/z$  = 431

**Example 92** (General procedure (B))

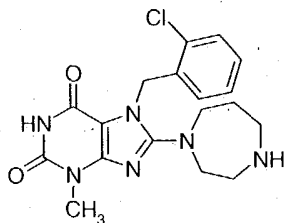
7-(2-Bromo-benzyl) -8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione. TFA



- $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  10.89 (s, 1H); 8.8 (s br, 2H); 7.74-6.74 (m, 4H); 5.37 (s, 2H); 3.66 (m, 2H); 3.40 (t, 2H); 3.35 (s, 3H); 3.26 (s br, 2H); 3.16 (s br, 2H); HPLC-MS  $m/z$  = 435

**Example 93** (General procedure (B))

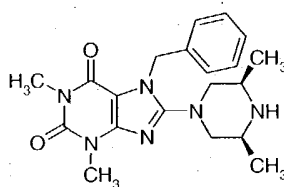
7-(2-Chloro-benzyl) -8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione. TFA



<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>):  $\delta$  10.88 (s, 1H); 8.83 (s br, 2H); 7.55-7.47 (m, 1H) 7.42-7.25 (m, 2H)  
 5 6.87-6.78 (m 1H); 5.43 (s, 2H); 3.66 (t, 2H); 3.41 (t, 2H); 3.35 (s, 3H); 3.27 (s br, 2H); 3.16  
 (s br, 2H); 1.95 (m, 2H). HPLC-MS *m/z* = 389

**Example 94** (General procedure (C))

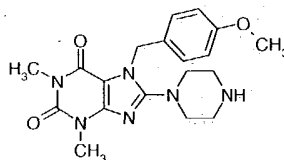
7-Benzyl-8-(3,5-dimethyl-piperazin-1-yl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione . 2HCl



10

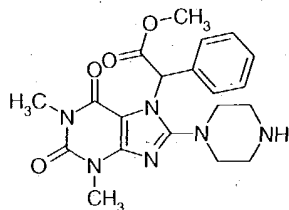
HPLC-MS (Method B): *m/z* = 383 (*m*+1); *R*<sub>t</sub> = 1.91 min.**Example 95** (General procedure (A))

7-(4-Methoxybenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

15 HPLC-MS (Method C) *m/z* = 384 (*M*+1); *R*<sub>t</sub> = 1.24 min.

**Example 96** (General procedure (A))

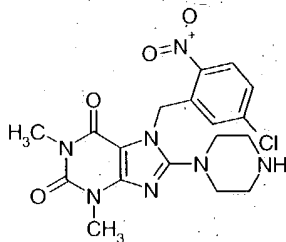
(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-yl) -phenylacetic acid methyl ester. TFA



5 HPLC-MS (Method C):  $m/z$  = 413 (M+1);  $R_t$  = 1.31 min.

**Example 97** (General procedure (A))

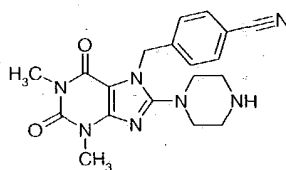
7-(5-Chloro-2-nitrobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA



HPLC-MS (Method C):  $m/z$  = 434 (M+1);  $R_t$  = 2.53 min. Purity = 100 % (ELS)

10 **Example 98** (General procedure (A))

4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzonitrile. TFA

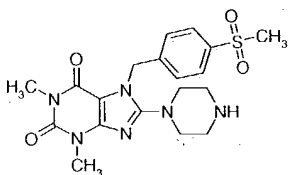


HPLC-MS (Method C)  $m/z$  = 380 (M+1);  $R_t$  = 1.21 min.

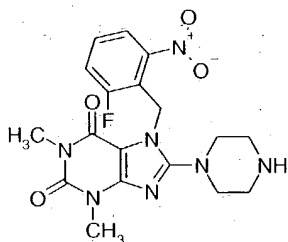
**Example 99** (General procedure (A))

7-(4-Methanesulfonylbenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione.

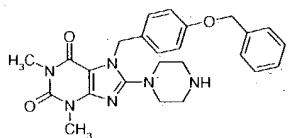
TFA

5 HPLC-MS (Method C)  $m/z = 433$  (M+1);  $R_t = 1.05$  min.**Example 100** (General procedure (A))

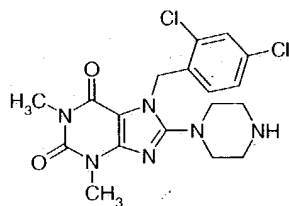
7-(2-Fluoro-6-nitrobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z = 418$  (M+1); 1.22 min.10 **Example 101** (General procedure (A))

7-(4-Benzyloxybenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z = 461$  (M+1);  $R_t = 1.82$  min.**Example 102** (General procedure (A))

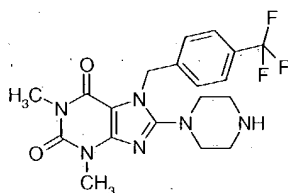
15 7-(2,4-Dichlorobenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z = 425$  (M+2);  $R_t = 1.57$  min. (Chlorine isotope signal)

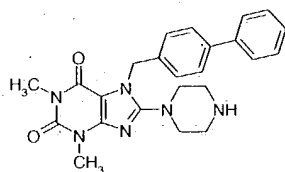
**Example 103** (General procedure (A))

1,3-Dimethyl-8-piperazin-1-yl-7-(4-trifluoromethylbenzyl) -3,7-dihydropurine-2,6-dione.

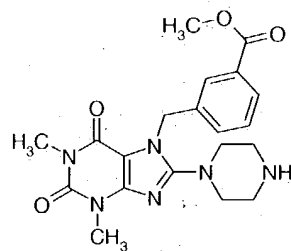
TFA

5 HPLC-MS (Method C)  $m/z = 423$  (M+1);  $R_t = 1.58$  min.**Example 104** (General procedure (A))

7-Biphenyl-4-ylmethyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

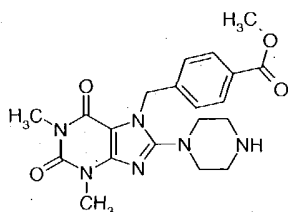
HPLC-MS (Method C)  $m/z = 431$  (M+1);  $R_t = 1.76$  min10 **Example 105** (General procedure (A))

3-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzoic acid methyl ester. TFA

HPLC-MS (Method C)  $m/z = 413$  (M+1);  $R_t = 1.33$  min.

**Example 106** (General procedure (A))

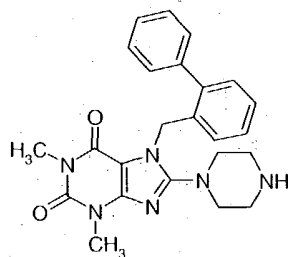
4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl) benzoic acid methyl ester. TFA



5 HPLC-MS (Method C)  $m/z = 413$  (M+1);  $R_t = 1.31$  min.

**Example 107** (General procedure (A))

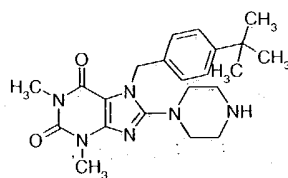
7-Biphenyl-2-ylmethyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA



HPLC-MS (Method C)  $m/z = 431$  (M+1);  $R_t = 1.55$  min.

10 **Example 108** (General procedure (A))

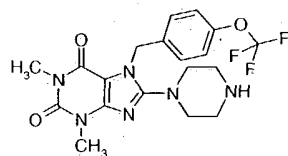
7-(4-tert-Butylbenzyl) -1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA



HPLC-MS (Method C)  $m/z = 411$  (M+1);  $R_t = 1.78$  min.

**Example 109** (General procedure (A))

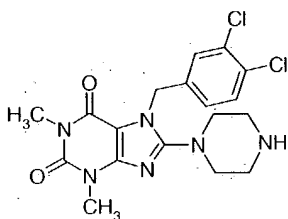
15 1,3-Dimethyl-8-piperazin-1-yl-7-(4-trifluoromethoxybenzyl) -3,7-dihydropurine-2,6-dione. TFA



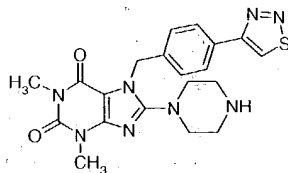
HPLC-MS (Method C)  $m/z = 439$  (M+1);  $R_t = 1.65$  min.

**Example 110** (General procedure (A))

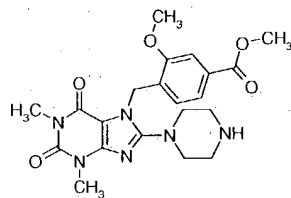
7-(3,4-Dichlorobenzyl)-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z$  = 424 (M+1);  $R_t$  = 2.87 min. Purity 98% (ELS)**5 Example 111** (General procedure (A))

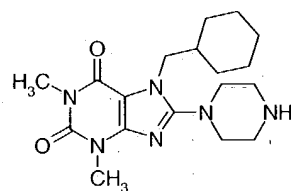
1,3-Dimethyl-8-piperazin-1-yl-7-(4-[1,2,3]thiadiazol-4-ylbenzyl)-3,7-dihydropurine-2,6-dione. TFA

HPLC-MS (Method C)  $m/z$  = 439 (M+1);  $R_t$  = 2.47 min. Purity 80% (ELS)**10 Example 112** (General procedure (A))

4-(1,3-Dimethyl-2,6-dioxo-8-piperazin-1-yl-1,2,3,6-tetrahydropurin-7-ylmethyl)-3-methoxybenzoic acid methyl ester. TFA

HPLC-MS (Method C)  $m/z$  = 443 (M+1);  $R_t$  = 2.50 min. Purity >99 % (ELS).**15 Example 113** (General procedure (A))

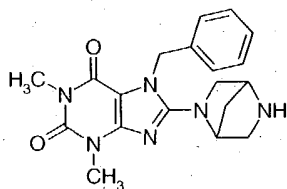
7-Cyclohexylmethyl-1,3-dimethyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione. TFA

HPLC-MS (Method B):  $m/z$  = 361 (M+1);  $R_t$  = 2.15 min.

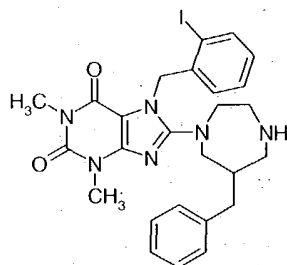
**Exempl 114** (General procedure (C))

7-Benzyl-8-(2,5-diaza-bicyclo[2.2.1]hept-2-yl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione.

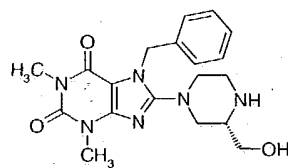
TFA

5 HPLC-MS (Method B):  $m/z$  = 367;  $R_t$  = 1.76 min. TIC area 100%**Example 115** (General procedure (A))

8-(6-Benzyl-[1,4]diazepan-1-yl) -7-(2-iodo-benzyl) -1,3-dimethyl-3,7-dihydro-purine-2,6-dione. TFA

10 HPLC-MS (Method B):  $m/z$  = 585 ( $M+1$ );  $R_t$  = 2.87 min; purity~50%**Example 116** (General procedure (A))

(S) -7-Benzyl-8-(3-hydroxymethylpiperazin-1-yl) -1,3-dimethyl-3,7-dihydropurine-2,6-dione



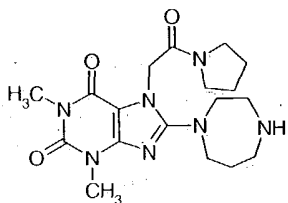
15 The piperazine moiety was prepared according to the general procedure for preparation of piperazine derivatives.

MeOH- $d_4$ ;  $\delta$  = 7.1-7.4 (m; 5H); 5.4 (d; 2H); 3.5 (s; 3H); 3.45 (m; 2H); 3.25 (s; 3H); 2.9-3.2 (m; 3H); 2.0 (m; 1H); 1.2 (s br; 3H). HPLC-MS (Method B):  $m/z$  = 385 ( $M+1$ );  $R_t$  = 1.65 min.



**Example 117** (General procedure (C))

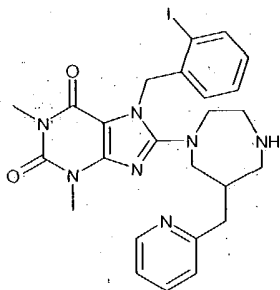
8-[1,4]Diazepan-1-yl-1,3-dimethyl-7-(2-oxo-2-pyrrolidin-1-yl-ethyl) -3,7-dihydro-purine-2,6-dione



5 HPLC-MS (Method B):  $m/z$  = 390;  $R_t$  = 2.93 min + 0.43 min; 43 + 56%

**Example 118** (General procedure (C))

7-(2-Iodo-benzyl)-1,3-dimethyl-8-(6-pyridin-2-ylmethyl-[1,4]diazepan-1-yl)-3,7-dihydro-purine-2,6-dione. TFA



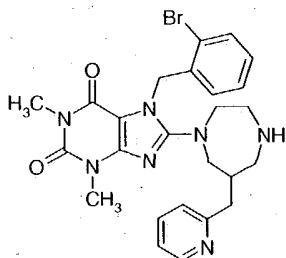
10

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.9 (s br, 2H); 8.65 (d, 1H); 8.2 (t, 1H); 7.85 (d, 1H); 7.15 (t, 1H); 7.5 (d, 1H); 7.3 (t, 1H); 7.0 (t, 1H); 6.75 (d, 1H); 5.45 (s, 2H); 3.05-3.8 (m, 3H); 3.5 (s, 3H); 3.3 (s, 4H); 2.8-3.25 (m, 7H). HPLC-MS (Method B):  $m/z$  = 586 ( $M+1$ );  $R_t$  = 2.25 min; Purity

15 (UV) = 97%.

**Example 119** (General procedure (A))

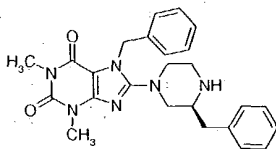
7-(2-Bromo-benzyl)-1,3-dimethyl-8-(6-pyridin-2-ylmethyl-[1,4]diazepan-1-yl)-3,7-dihydro-purine-2,6-dione



HPLC-MS (Method B):  $m/z$  = 538 & 541 ( $M+1$ ;  $M+2$ );  $R_t$  = 1.94 min

**5 Example 120** (General procedure (D))

(S) 7-Benzyl-8-(3-benzyl-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione

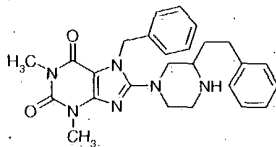


$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.24(m, 10H); 5.32(m, 2H); 3.52(s, 3H); 3.11(m, 11H); 2.68(m, 2H).

HPLC-MS (Method B):  $m/z$  = 445 ( $M+1$ ), 354, 263;  $R_t$  = 4.13

**10 Example 121** (General procedure (D))

7-Benzyl-1,3-dimethyl-8-(3-phenethyl-piperazin-1-yl)-3,7-dihydro-purine-2,6-dione

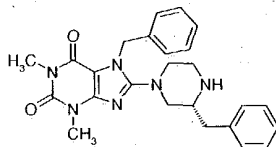


$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  7.25(m, 10H); 5.41(s, 2H); 3.30(m, 15H); 1.88(m, 2H). HPLC-MS.

(Method B):  $m/z$  = 481( $M+\text{Na}$ ), 459/460( $M+1$ );  $R_t$  = 2.52 min.

**15 Example 122** (General procedure (D))

(R)-7-Benzyl-8-(3-benzylpiperazin-1-yl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione

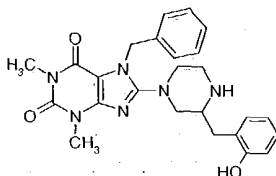


$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.24(m, 10H); 5.34(m, 2H); 3.55(s, 3H); 3.34(m, 5H); 2.78(m, 7H);

1.70(s, 1H). HPLC-MS (Method B):  $m/z$  = 445/446( $M+1$ ), 468( $M+\text{Na}$ );  $R_t$  = 2.56 min.

**Example 123** (General procedure (D))

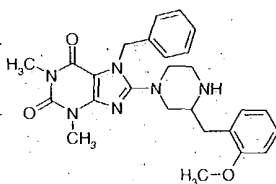
7-Benzyl-8-(3-(2-hydroxy-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione



- 5  $^1\text{H-NMR}$  ( $\text{MeOH-}d_4$ ):  $\delta$  7.28(m, 3H); 7.11(m, 4H); 6.81(m, 2H); 5.43(m, 2H); 3.70(m, 1H); 3.31(m, 14H); 2.88(s, 2H). HPLC-MS (Method B):  $m/z$  = 461/462( $m+1$ ); 483( $M+\text{Na}$ );  $R_t$  = 2,409

**Example 124** (General procedure (D))

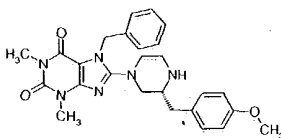
7-Benzyl-8-(3-(2-methoxy-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione



- $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.22(m, 7H); 6.87(m, 2H); 5.32(m, 2H); 3.83(s, 3H); 3.54(s, 3H); 3.33(m, 5H); 2.79(m, 7H); 1.87(s, 1H) HPLC-MS (Method B):  $m/z$  = 475,476,477 ( $M+1$ );  $R_t$  = 2.57

**Example 125** (General procedure (D))

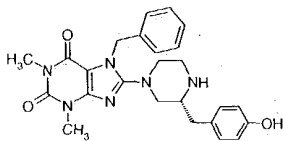
(R) 7-Benzyl-8-(3-(4-methoxy-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione



- $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.25(m, 5H); 7.08(m, 2H); 6.84(m, 2H); 5.34(m, 2H); 3.80(s, 3H); 3.55(s, 3H); 3.38(s, 3H); 3.29(m, 2H); 2.88(m, 5H); 2.52(m, 2H); 1.64(s, 1H) HPLC-MS (Method B):  $m/z$  = 497( $M+1$ ), 475/476/477( $M+1$ );  $R_t$  = 2,368min

**Example 126** (General procedure (D))

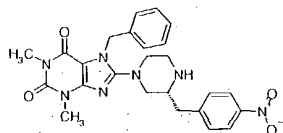
(R)-7-Benzyl-8-(3-(4-hydroxy-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione



5  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  9.38(s, 1H); 8.86(s, 2H); 7.29(m, 3H); 7.13(m, 2H); 6.98(m, 2H); 6.72(m, 2H); 5.36(m, 2H); 3.09(m, 15H) HPLC-MS (Method B):  $m/z$  = 943(2M+Na), 461/462(M+1);  $R_t$  = 2.017

**Example 127** (General procedure (D))

10 (R)-7-Benzyl-1,3-dimethyl-8-(3-(4-nitro-benzyl)-piperazin-1-yl)-3,7-dihydro-purine-2,6-dione

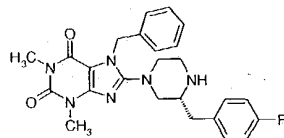


$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.17(m, 2H); 7.30(m, 7H); 5.34(s, 2H); 3.55(s, 3H); 3.00(m, 12H) HPLC-MS (Method B):  $m/z$  = 490/491(M+1);  $R_t$  = 2.522

15

**Example 128** (General procedure (D))

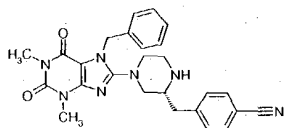
(R)-7-Benzyl-8-(3-(4-fluoro-benzyl)-piperazin-1-yl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione



20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.32(m, 2H); 7.08(m, 7H); 5.34(m, 2H); 3.55(m, 3H); 2.93(m, 12H) HPLC-MS (Method B):  $m/z$  = 947(2M+Na), 485(M+Na), 463/464(M+1)  $R_t$  = 2,35 min

**Example 129** (General procedure (D))

(R)-4-(4-(7-Benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)-piperazin-2-ylmethyl)-benzonitrile

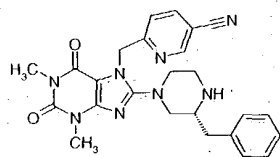


5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.61(m, 2H); 7.26(m, 7H); 5.34(s, 2H); 3.53(s, 3H); 3.28(m, 5H); 2.83(m, 7H)

HPLC-MS (Method B):  $m/z$  = 492(M+Na), 470/471 (M+1);  $R_t$  = 2.334

**Example 130** (General procedure (D))

10 (R)-6-(8-(3-Benzyl-piperazin-1-yl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl)-nicotinonitrile



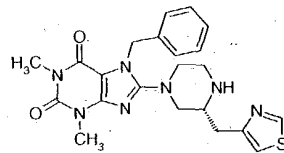
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.67(m, 1H); 7.88(m, 1H); 7.22(m, 6H); 5.40(s, 2H); 3.55(m, 3H);

3.33(m, 5H); 2.85(m, 7H) HPLC-MS (Method B):  $m/z$  = 963(2M+Na), 471/472(M+1);  $R_t$  =

15 1.791 min.

**Example 131** (General procedure (D))

(R)-7-Benzyl-1,3-dimethyl-8-(3-thiazol-4-ylmethyl-piperazin-1-yl)-3,7-dihydro-purine-2,6-dione

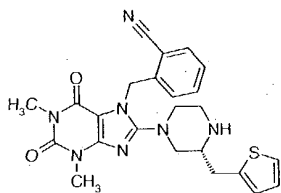


20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.77(m, 1H); 7.26(m, 5H); 7.02(m, 1H); 5.35(m, 2H); 3.54(s, 3H);

2.74(m, 12H) HPLC-MS (Method B):  $m/z$  = 452/453(M+1)  $R_t$  = 2.220 min.

**Example 132** (General procedure (D))

(R)-2-[1,3-Dimethyl-2,6-dioxo-8-(3-thiophen-2-ylmethyl-piperazin-1-yl)-1,2,3,6-tetrahydropurin-7-ylmethyl]-benzonitrile



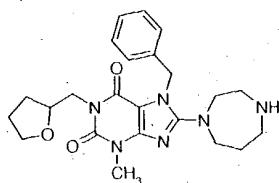
- 5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.70(s, 1H); 7.55(s, 1H); 7.40(s, 1H); 7.13(s, 2H); 6.88(s, 3H); 5.56(s, 2H); 3.58(s, 3H); 2.96(m, 12H) HPLC-MS (Method B): Ret.time=2.40 min.  $m/z$  = 489(M+Na), 476/477(M+1)

By use of the general methods described above, the following compounds can furthermore be made:

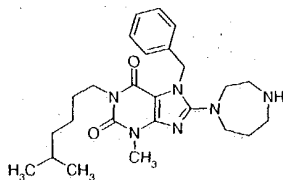
10

**Example 133**

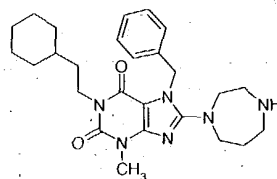
7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(tetrahydro-furan-2-ylmethyl)-3,7-dihydro-purine-2,6-dione

**Example 135**

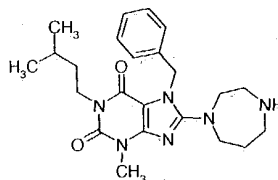
7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(5-methyl-hexyl)-3,7-dihydro-purine-2,6-dione

**Example 134**

7-Benzyl-1-(2-cyclohexyl-ethyl)-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione

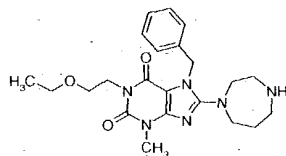
**Example 136**

7-Benzyl-8-[1,4]diazepan-1-yl-3-methyl-1-(3-methyl-butyl)-3,7-dihydro-purine-2,6-dione

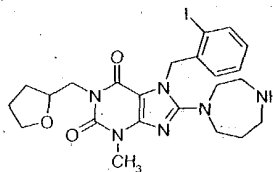


**Example 137**

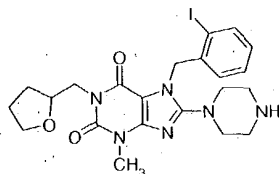
7-Benzyl-8-[1,4]diazepan-1-yl-1-(2-ethoxy-ethyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 138**

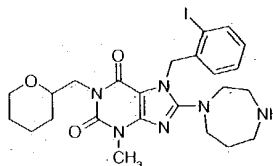
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-(tetrahydro-furan-2-ylmethyl)-3,7-dihydro-purine-2,6-dione

**Example 139**

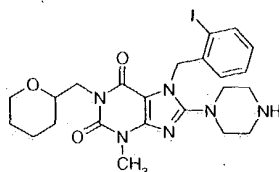
7-(2-Iodo-benzyl)-3-methyl-8-piperazin-1-yl-1-(tetrahydro-furan-2-ylmethyl)-3,7-dihydro-purine-2,6-dione

**Example 140**

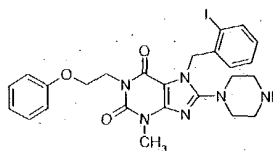
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-(tetrahydro-pyran-2-ylmethyl)-3,7-dihydro-purine-2,6-dione

**Example 141**

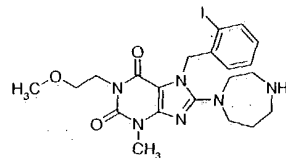
7-(2-Iodo-benzyl)-3-methyl-8-piperazin-1-yl-1-(tetrahydro-pyran-2-ylmethyl)-3,7-dihydro-purine-2,6-dione

**Example 142**

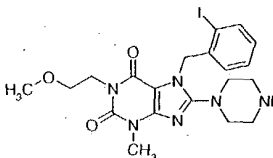
7-(2-Iodo-benzyl)-3-methyl-1-(2-phenoxy-ethyl)-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 143**

8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-1-(2-methoxy-ethyl)-3-methyl-3,7-dihydro-purine-2,6-dione

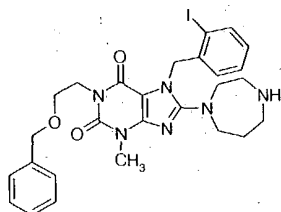
**Example 144**

7-(2-Iodo-benzyl)-1-(2-methoxy-ethyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

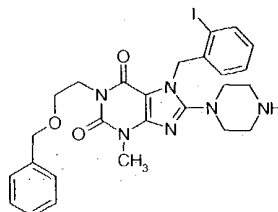


**Example 145**

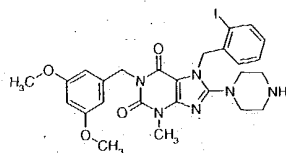
1-(2-Benzyloxy-ethyl)-8-[1,4]diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 146**

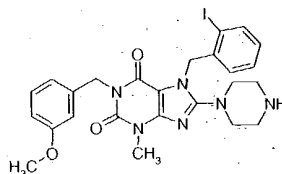
1-(2-Benzyloxy-ethyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 147**

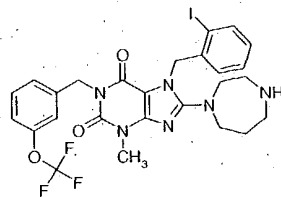
1-(3,5-Dimethoxy-benzyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 148**

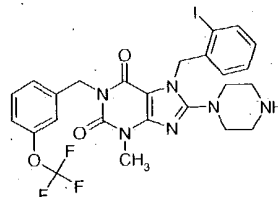
7-(2-Iodo-benzyl)-1-(3-methoxy-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 149**

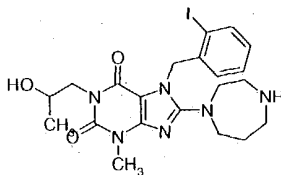
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-(3-trifluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione

**Example 150**

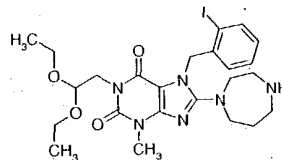
7-(2-Iodo-benzyl)-3-methyl-8-piperazin-1-yl-1-(3-trifluoromethoxy-benzyl)-3,7-dihydro-purine-2,6-dione

**Example 151**

8-[1,4]Diazepan-1-yl-1-(2-hydroxy-propyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 152**

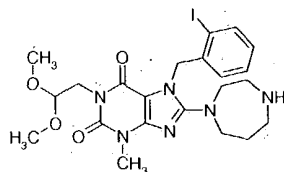
8-[1,4]Diazepan-1-yl-1-(2,2-diethoxy-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione



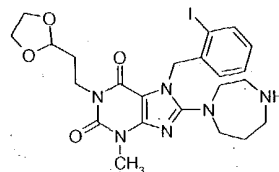


**Example 153**

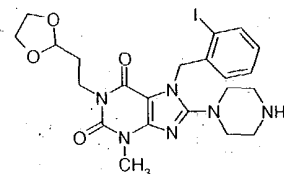
8-[1,4]Diazepan-1-yl-1-(2,2-dimethoxy-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 154**

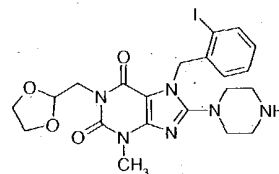
8-[1,4]Diazepan-1-yl-1-(2-[1,3]dioxolan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 155**

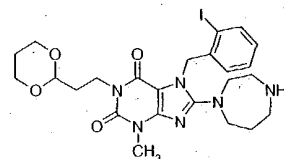
1-(2-[1,3]Dioxolan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 156**

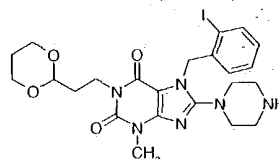
1-[1,3]Dioxolan-2-ylmethyl-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 157**

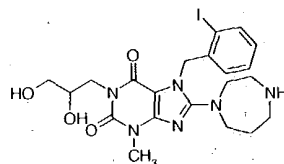
8-[1,4]Diazepan-1-yl-1-(2-[1,3]dioxan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 158**

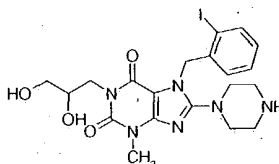
1-(2-[1,3]Dioxan-2-yl-ethyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 159**

8-[1,4]Diazepan-1-yl-1-(2,3-dihydroxy-propyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

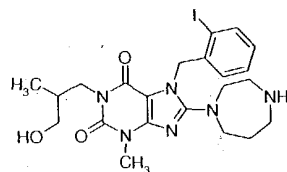
**Example 160**

1-(2,3-Dihydroxy-propyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

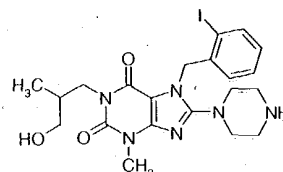


**Example 161**

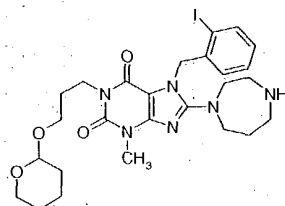
8-[1,4]Diazepan-1-yl-1-(3-hydroxy-2-methyl-propyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 162**

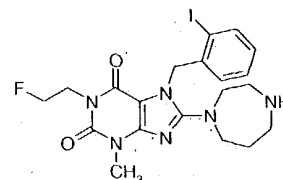
1-(3-Hydroxy-2-methyl-propyl)-7-(2-iodo-benzyl)-3-methyl-8-piperazin-1-yl-3,7-dihydro-purine-2,6-dione

**Example 163**

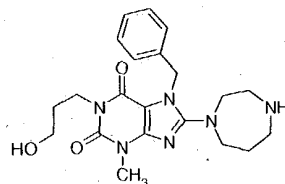
8-[1,4]Diazepan-1-yl-7-(2-iodo-benzyl)-3-methyl-1-[3-(tetrahydro-pyran-2-yloxy)-propyl]-3,7-dihydro-purine-2,6-dione

**Example 164**

8-[1,4]Diazepan-1-yl-1-(2-fluoro-ethyl)-7-(2-iodo-benzyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 165**

7-Benzyl-8-[1,4]diazepan-1-yl-1-(3-hydroxy-propyl)-3-methyl-3,7-dihydro-purine-2,6-dione

**Example 166**

7-Biphenyl-2-ylmethyl-8-[1,4]diazepan-1-yl-3-methyl-3,7-dihydro-purine-2,6-dione

